Antiplatelet therapy and the risk of hepatocellular carcinoma in chronic hepatitis B patients on antiviral treatment

Short title: Antiplatelet Therapy and Hepatocellular Carcinoma

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Abbreviations:

CHB, chronic hepatitis B; CI, confidence interval; CTP, Child-Turcotte-Pugh; CU-HCC, Chinese University-HCC; GAG-HCC. Guide with Age, Gender; HBV DNA, Core Promoter Mutations and Cirrhosis-HCC ; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, model for end-stage liver disease.

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ABSTRACT

Antiplatelet therapy has shown protective effects against hepatocellular carcinoma (HCC) in preclinical studies. However, it is unclear whether antiplatelet therapy lowers the risk of HCC in patients with chronic hepatitis B (CHB). A retrospective analysis was conducted of data from 1,674 CHB patients, enrolled between January 2002 and May 2015, whose serum hepatitis B virus (HBV) DNA levels were suppressed by antivirals to <2,000 IU/mL. The primary and secondary outcomes were development of HCC and bleeding events, respectively. Risk was compared between patients with antiplatelet treatment (aspirin, clopidogrel, or both; antiplatelet group) and patients who were not treated (non-antiplatelet group) using a time-varying Cox proportional hazards model for total population and propensity score-matching analysis. The antiplatelet group included 558 patients and the non-antiplatelet group had 1,116 patients. During the study period, 63 patients (3.8%) developed HCC. In time-varying Cox proportional analyses, the antiplatelet group showed a significantly lower risk of HCC (hazard ratio [HR]: 0.44; 95% confidence interval [CI]: 0.23–0.85, *P*=0.01), regardless of antiplatelet agent. In propensity score-matched pairs, antiplatelet therapy significantly reduced the risk of HCC (HR: 0.34, 95% CI: 0.15–0.77, *P*=0.01). However, the overall risk of bleeding was higher in the antiplatelet group (HR: 3.28, 95% CI: 1.98–5.42, *P*<0.001), particularly for clopidogrel with or without aspirin. Treatment with aspirin alone was not associated with a higher bleeding risk (HR: 1.11, 95% CI: 0.48–2.54, *P*=0.81). ***Conclusions*:** Antiplatelet therapy reduces the risk of HCC in CHB patients whose HBV is effectively suppressed. However, antiplatelet therapy containing clopidogrel may increase the risk of bleeding.

Introduction

Chronic hepatitis B virus (HBV) infection is a major global health burden. Approximately 400 million people worldwide are chronically infected with HBV (1, 2). These patients have a substantially increased risk of cirrhosis and hepatocellular carcinoma (HCC), which together are responsible for approximately 1 million deaths worldwide every year (1, 2). Despite the use of highly potent antivirals, such as entecavir and tenofovir which may effectively reduce the risk of HCC (3, 4), long-term follow-up studies have showed that approximately 1–8% of patients with cirrhosis develop HCC per year (5, 6). Beyond the preventive effects of potent antiviral agents, chemopreventive strategies aimed at decreasing the risk or delaying the onset of HCC are needed in the era of antiviral therapy (7).

Recent preclinical studies have suggested potential therapeutic applications of antiplatelet therapy in hepatitis B models. Platelets are key facilitators of this immune-mediated injury, as they promote accumulation of $CD8^+$ T cells (8). In an HBV transgenic mouse model of chronic immune-mediated liver disease that rapidly progresses to HCC, aspirin and/or clopidogrel reportedly decreased T-cell-mediated inflammation, fibrosis severity, and progression to HCC (9). In epidemiological studies, however, the effect of aspirin on HCC prevention is controversial. A large population-based study in the National Institutes of Health Association of American Retired Persons Diet and Health Study cohort showed that aspirin use was associated with a 41% lower risk of HCC compared to non-use (10). By contrast, other population-based case–control and cohort studies have not observed an association between aspirin use and risk of HCC due to any cause, although these studies were not specifically designed to focus on aspirin use and HCC (11, 12). In addition, previous epidemiological studies have had critical limitations to drawing concrete conclusions given that important confounders, such as age, gender, cirrhosis status, and antiviral treatments in

chronic hepatitis B (CHB) patients, were not adequately controlled.

We investigated whether antiplatelet therapy is associated with a reduction in HCC incidence in CHB patients with HBV, which is one of the most important risk factors in developing HCC (13), effectively suppressed by nucleos(t)ide analogs.

Materials and Methods

Study Design

The study population was obtained from inpatient and outpatient database files between November 1, 2002 and May 31, 2015 at Seoul National University Hospital (Seoul, Korea) and consisted of a cohort of 14,392 consecutive adult CHB patients with suppressed HBV (serum HBV DNA levels<2,000 IU/mL) via antiviral treatment (Fig. 1). Patients were excluded if they met any of the following criteria: younger than age 18 or older than age 85; HCC development within 6 months from the index date; diagnosis with HCC before study enrollment; hepatitis B surface antigen seroclearance within 6 months from the index date; co-infection with other hepatotrophic viruses or human immunodeficiency virus; duration of antiplatelet or antiviral therapy<6 months, Previous or current treatment with any other potentially confounding drugs, such statins, metformin, sulfonylurea, insulin, or non-steroidal anti-inflammatory drugs except aspirin for more than 1 month; serum HBV DNA levels≥2,000 IU/mL at enrollment; or active alcoholism. To minimize the potential confounding effects of an antiviral regimen on HCC development, any patients who had been treated with antiviral agents that were never used in the antiplatelet group, such as pegylated interferon-α, or clevudine- or tenofovir disoproxil fumarate (TDF)-containing regimens, were excluded from the non-antiplatelet group. None of patients in the antiplatelet group were treated with pegylated interferon-α, or clevudine- or TDF-containing regimens.

The entire cohort was divided according to antiplatelet therapy: the non-antiplatelet group consisted of patients treated with various antiviral agents and the antiplatelet group was patients who were treated with antiplatelets (aspirin 100 mg/day, clopidogrel 75 mg/day, or both) and antiviral agents. All antiplatelet agents were prescribed by the physicians at Seoul National University Hospital for the patients visiting the outpatient clinic on a regular basis.

We excluded patients in the non-antiplatelet group who had taken aspirin, including over-the-counter (OTC) drugs containing aspirin, for more than 1 month before the index date, based on both medical history taken in the outpatient clinic and data in the questionnaire on medication history in the patient's file in the outpatient or inpatient clinic. During the study period, patients in the non-antiplatelet group who had taken aspirin or OTC drugs containing aspirin for more than 1 month were also excluded, based on the questionnaire used to screen for medications with high bleeding risk (e.g. antiplatelets and anticoagulants) before endoscopic surveillance every 1 to 2 years for esophageal varix or gastric cancer.

The patients in the non-antiplatelet group were randomly selected from the database file with matching to the antiplatelet group (2:1 ratio) by the presence of cirrhosis. This study was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for informed consent from patients was waived.

Endpoints and Follow-up Evaluation

The primary endpoint of interest in this study was HCC development. Secondary endpoints evaluated included bleeding events, bleeding-related mortality, and the development of malignancy other than HCC, end-stage kidney disease, and cardiovascular events. The index date was defined as the first date that the patient on antiviral treatment achieved a serum level of HBV DNA<2,000 IU/mL. The censored date was defined as the date of patient's death, last date of follow-up, or data cutoff date (May 31, 2015).

Patients regularly underwent clinical examinations, liver function tests, and measurement of serum HBV DNA levels every 6 months. The main modality for HCC surveillance in this study was ultrasonography with serum alpha-fetoprotein (AFP) levels according to the current guidelines of this country (14). Compliance of taking antiviral agents was confirmed

by both meticulous reviews of medical records written by physicians who prescribed the agents and serial follow up of HBV DNA titer every 6 months (15). When results of surveillance tests were equivocal, 3-month interval screenings were permitted. Compliance with antiplatelet agents in the antiplatelet group was assessed when the patients visited the outpatient clinic where physicians had first prescribed antiplatelet agents such as the departments of cardiology, endocrinology, neurology, family medicine, and neurosurgery. To evaluate patient compliance with antiplatelet agents, we calculated the medical possession rates (MPRs) of the patients in the antiplatelet group stratified by specific antiplatelet therapy and determined the median MPR values. MPR was calculated by the total days of medication supply divided by time interval. We used an MPR cutoff value for good compliance of >80% (16). PAGE-B scores (17), developed for HCC risk assessment in CHB patients under effective antiviral therapy, were used to stratify the risk of developing HCC at baseline in both groups.

Definitions

Diagnosis of liver cirrhosis and HCC was described in the Supplementary Document 1 and bleeding events were defined in the Supplementary Document 2. Viral breakthrough during follow-up was defined as an increase in HBV DNA by >1 log compared to nadir or HBV DNA 100 IU/mL in patients on antiviral therapy with previously undetectable levels (18). Serum assays were also described in the Supplementary Document 3.

Statistical Analyses

A time-varying Cox proportional hazards regression model, propensity score matching, and competing risk analyses were performed. Detail statistical analyses were described in the

Supplementary Document 4.

Results

Baseline Characteristics

The total study population was comprised of 1,674 CHB patients: 1,116 patients were on antivirals only without antiplatelets (non-antiplatelet group) and 558 patients were taking antiplatelet therapy in addition to antiviral treatment (antiplatelet group) (Fig. 1).

The two groups differed significantly in terms of baseline characteristics (Table 1). Patients in the non-antiplatelet group were significantly younger (mean, 50 vs. 55 years), had a higher HBeAg-positivity rate (24.4% vs. 14.5%), and lower serum HBV DNA levels (mean, 1.5 vs. 1.4 $\log_{10}$ IU/mL) compared to those in the antiplatelet group. The MELD scores in the antiplatelet group were significantly higher than those in the non-antiplatelet group. There were no significant differences between the numbers of patients taking each type of antiviral treatment (Supplementary Table 1). In the antiplatelet group, the median duration of exposure to antiplatelet therapy was 27.6 months (interquartile range [IQR], 7.2–60.5 months): the median duration of exposure to antiplatelets among patients treated with aspirin, clopidogrel, or dual antiplatelet therapy of aspirin plus clopidogrel was 38.5 months (IQR, 10.4–68.7 months), 17.3 months (IQR, 6.0–36.7 months), and 18.0 months (IQR, 6.0–47.1 months), respectively. The main purpose of taking antiplatelet agents was the prevention of cardiovascular disease (42.1%). In particular, patients mainly took aspirin for preventive purposes (56.1%). Clopidogrel alone or dual antiplatelet treatment with both aspirin and clopidogrel was prescribed mainly after percutaneous coronary intervention for ischemic heart disease (32.2% and 59.2%, respectively). The median MPRs for the patients treated with aspirin, clopidogrel, or dual antiplatelet were 88.3% (IQR 72.2%–99.1%), 82.7% (IQR 71.6%–95.3%), and 81.5% (IQR 70.5%–96.2%), respectively.

The probable etiologies for serum ALT levels exceeding 80 U/L were as follows: non-

alcoholic fatty liver disease (NAFLD; n=81), drug-induced liver injury (n=25), ischemic hepatitis (n=2), and congestive cardiac failure (n=6).

The interval between each surveillance by ultrasonography with serum AFP levels in the non-antiplatelet group was 6.1 ± 1.9 months, which was not significantly different from 6.2 ± 1.3 months in the antiplatelet group (*P*=0.51; Supplementary Table 2). When hepatic nodules that were suspicious for HCC were detected during ultrasonography, serum AFP levels were rising, or the results of the ultrasonography exam were incomplete due to cirrhotic liver parenchyma, contrast-enhanced liver computed tomography (CT) and/or liver-specific contrast-enhanced magnetic resonance imaging (MRI) were performed. The proportion of patients examined by contrast-enhanced liver CT plus liver-specific contrast-enhanced MRI was not significantly different between non-antiplatelet and antiplatelet groups.

Clinical Events during Study Period

During the study period (median, 57 months; IQR, 31–93 months), a total of 63 (3.8%) patients developed HCC. For patients with HCC in this study, a significant difference in HCC stages according to Barcelona Clinic Liver Cancer staging systems and treatment modalities between antiplatelet and non-antiplatelet groups was not found (Supplementary Tables 3 and 4). Among 1,611 patients without HCC development, 90 (5.6%) expired and 17 (1.1%) underwent liver transplantation. Among 63 patients with HCC development, 4 (6.3%) patients expired and 1 (1.6%) patients underwent liver transplantation.

Viral breakthrough occurred in 126 (11.3%) of the 1,116 non-antiplatelet patients and 50 (9.0%) of the 558 antiplatelet patients (*P*=0.14) (not shown as a table). Among the 1,116 non-antiplatelet patients, 35 (3.1%) of the patients with viral breakthrough showed poor compliance and 91 (8.2%) showed drug resistance; among the 558 antiplatelet, patients 25

(4.5%) of the patients with viral breakthrough showed poor compliance and 25 (4.5%) showed drug resistance. The patients with antiviral resistance achieved complete virologic suppression after their antiviral regimen was changed to rescue therapy with nucleos(t)ide analogs.

Association between Antiplatelet Therapy and HCC Development

Multivariable Analyses

To minimize the immortal time bias, time-varying Cox regression analyses to identify factors predictive of HCC development were performed for the entire cohort (n=1,674) (Table 2). Antiplatelet therapy overall was independently associated with a significantly lower risk of HCC development (hazard ratios [HR]: 0.44, 95% confidence interval [CI]: 0.23–0.85, *P*=0.01) after adjustment for age, platelet counts, and viral breakthrough (Table 2). The cumulative incidence rates of HCC were 1.6% at 5 years for patients in the antiplatelet group and 5.2% in the non-antiplatelet group (Fig. 2A). Regarding respective antiplatelet agents, the aspirin treatment showed an independent association with a significantly lower risk of HCC development (HR: 0.26, 95% CI: 0.09–0.74, *P*=0.01). However, neither clopidogrel group (HR: 0.63, 95% CI: 0.15–2.65, *P*=0.53) nor dual antiplatelets (HR: 0.67, 95% CI: 0.28–1.60, *P*=0.37) group showed significant association with a risk of HCC development (Table 2). The cumulative incidence rates of HCC at 5 years were 1.6%, 1.3%, and 1.8% in aspirin, clopidogrel, and dual antiplatelets groups, respectively (Fig. 2B).

The primary diagnosis of HCC in the other patients (237 patients, 14.2%) lost to follow-up was identified using data obtained from the Korean National Health Insurance Service database. Among patients in the antiplatelet group, 41 patients (7.3%) were lost to follow-up; 196 patients (17.6%) in the non-antiplatelet group were lost to follow-up. When those

patients were included in both groups, the risk of HCC development in the antiplatelet group was significantly lower than that in the non-antiplatelet group (HR: 0.45, 95% CI: 0.24–0.86, *P*=0.008) (not shown as a table). Regarding respective antiplatelet agents, the aspirin group (HR: 0.28, 95% CI: 0.11–0.75, *P*=0.009) was significantly associated with a lower risk of HCC. Additionally, both clopidogrel (HR: 0.65, 95% CI: 0.16–2.64, *P*=0.55) and dual antiplatelets groups (HR: 0.68, 95% CI: 0.29–1.58, *P*=0.38) displayed a lower risk for HCC development, but failed to reach statistical significance.

Viral breakthrough was independently associated with a significantly higher risk of HCC development (HR: 2.46, 95% CI: 1.36–4.46, *P*=0.003) (Table 2). In subgroup of patients who did not experience viral breakthrough during study period, antiplatelet therapy (n=508) was significantly associated with lower development of HCC compared to the non-antiplatelet group (n=990) (HR: 0.48, 95% CI: 0.23–0.97, *P*=0.04) (Supplementary Table 5). Regarding respective antiplatelet agents, the aspirin group (HR: 0.27, 95% CI: 0.08–0.85, *P*=0.03) was significantly associated with lower risk of HCC. Both clopidogrel (HR: 1.02, 95% CI: 0.25–4.18, *P*=0.98) and dual antiplatelets groups (HR: 0.71, 95% CI: 0.26–1.96, *P*=0.50) failed to reach statistical significance. However, among patients who experienced viral breakthrough, antiplatelet therapy (n=50) was not significantly associated with lower development of HCC compared to the non-antiplatelet group (n = 126) (HR: 0.87, 95% CI: 0.25–3.04, *P*=0.83) (Supplementary Table 5). Respective antiplatelet agents were not significantly associated with lower development of HCC compared to the non-antiplatelet group: the aspirin group (HR: 0.72, 95% CI: 0.08–2.92, *P*=0.70); the clopidogrel group (HR: 2.29, 95% CI: 0.02–15.97, *P*=0.61); and the dual antiplatelets group (HR: 2.15, 95% CI: 0.41–7.06, *P*=0.32).

When the causes of antiplatelet therapy were considered in the development of HCC, coronary heart disease, arrhythmia, and brain infarcts were found not to be independent

predictors in this study (Supplementary Document 5). A significant association between antiplatelet therapy and lower HCC development was maintained after adjusting for the three factors.

Analyses after Balancing the Two Groups

Propensity score matching of the entire study population yielded 420 matched pairs of patients. Non-antiplatelet and antiplatelet groups within this matched cohort did not significantly differ in their baseline characteristics (Table 3). In the propensity score-matched cohort, the risk of HCC development in the antiplatelet group was significantly lower than in the non-antiplatelet group (HR: 0.34, 95% CI: 0.15–0.77, *P*=0.01; Supplementary Table 6). The 5-year cumulative incidence rates of HCC were 1.4% in the antiplatelet group and 9.9% in the non-antiplatelet group (Fig. 2C). Regarding respective antiplatelet agents, aspirin (HR: 0.07, 95% CI: 0.02–0.24, *P*<0.001), clopidogrel (HR: 0.11, 95% CI: 0.01–0.80, *P*=0.03), and dual antiplatelets groups (HR: 0.11, 95% CI: 0.03–0.46, *P*=0.002) were associated with a significantly lower risk of HCC development than the non-antiplatelet group, respectively. In patients treated with aspirin, clopidogrel, and dual antiplatelets, the cumulative incidence rates of HCC at 5 years were 1.3%, 1.8%, and 1.4%, respectively (Fig. 2D).

With regard to patients who did not experience viral breakthrough in propensity score matching analysis, antiplatelet therapy was significantly associated with a lower risk of HCC compared to the non-antiplatelet group (HR: 0.20, 95% CI: 0.07–0.56, *P*=0.002; Supplementary Table 6). Regarding respective antiplatelet agents, the aspirin group (HR: 0.16, 95% CI: 0.04–0.68, *P*=0.01) was significantly associated with a lower risk of HCC. Both clopidogrel (HR: 0.44, 95% CI: 0.06–3.24, *P*=0.42) and dual antiplatelets groups (HR: 0.17, 95% CI: 0.02–1.27, *P*=0.09) exhibited a lower risk of HCC, but failed to reach statistical

significance. However, of patients who exhibited viral breakthrough, antiplatelet therapy was not significantly associated with a lower development of HCC compared to the non-antiplatelet group (HR: 0.62, 95% CI: 0.18–2.16, *P*=0.45). Regarding respective antiplatelet agents, a significant difference in the risk of HCC development in each treatment group compared to the non-antiplatelet group was not observed: aspirin (HR: 0.49, 95% CI: 0.05–1.99, *P*=0.36), clopidogrel (HR: 2.58, 95% CI: 0.02–18.57, *P*=0.57), and dual antiplatelets groups (HR: 1.49, 95% CI: 0.29–4.91, *P*=0.59).

Competing Risk Analyses

The three competing outcomes in this study were death, transplantation, and HCC. It is possible that the more frequent occurrences of death or transplantation in the antiplatelet group may have reduced the number of patients at risk for HCC. Thus, risks were adjusted using competing risk analysis (competing events for death and transplantation) in both the entire cohort and the propensity score-matched cohort. In the entire cohort, HCC risk in the antiplatelet group was significantly higher than in the non-antiplatelet group (HR: 0.27, 95% CI: 0.14–0.52, *P*<0.001). Regarding respective antiplatelet agents, the aspirin group showed a significantly lower risk of HCC than the non-antiplatelet group (HR: 0.21, 95% CI: 0.09–0.48, *P*<0.001). The clopidogrel (HR: 0.32, 95% CI: 0.08–1.33, *P*=0.12) and dual antiplatelets groups (HR: 0.42, 95% CI: 0.16–1.05, *P*=0.06) had lower risk, but failed to reach statistical significance (Supplementary Fig. 1). In the propensity score-matched cohort, HCC risk in the antiplatelet group was significantly higher than in the non-antiplatelet group (HR: 0.08, 95% CI: 0.03–0.21, *P*<0.001). All the respective antiplatelet agents showed a significantly lower risk of HCC than the non-antiplatelet group: aspirin (HR: 0.06, 95% CI: 0.02–0.21, *P*<0.001), clopidogrel (HR: 0.11, 95% CI: 0.01–0.81, *P*=0.03), and dual antiplatelets (HR: 0.11, 95%

CI: 0.03–0.46, *P*=0.002), respectively.

During a median period of 4.8 years, HCC-related mortality rates in the antiplatelet group were not significantly different from those in the non-antiplatelet group (HR: 0.31, 95% CI: 0.07–1.32, *P*=0.11) after competing risk analysis (competing events for HCC-unrelated death and liver transplantation). The 5-year mortality rates were 1.6% in the antiplatelet group and 1.5% in the non-antiplatelet group, respectively (Supplementary Fig. 2).

Subgroup Analyses According to HCC Risk Models

When we compared the predictive performance of CU-HCC, modified GAG-HCC, REACH-B, and PAGE-B scores for HCC development, all four HCC risk scores showed an acceptable predictive function (all concordance indices ≥0.73; Supplementary Table 7). According to HCC risk stratification by PAGE-B score, intermediate- or high-risk patients in the antiplatelet group (Fig. 2E) had a significantly lower risk for HCC compared to intermediate- or high-risk patients in the non-antiplatelet group (Fig. 2F): intermediate-risk in the antiplatelet group vs. intermediate-risk in the non-antiplatelet group (HR: 0.34, 95% CI: 0.13–0.79, *P*=0.02); high-risk in the antiplatelet group vs. high-risk in the non-antiplatelet group (HR: 0.32, 95% CI: 0.13–0.69, *P*=0.007) (Supplementary Table 8). In low-risk patients, there was no significant difference of HCC development between the antiplatelet and non-antiplatelet groups (HR: 0.13, 95% CI: 0.00–1.43, *P*=0.20).

In subgroup analyses according to the other three HCC risk models (CU-HCC, modified GAG-HCC, and REACH-B), antiplatelet therapy was significantly or marginally associated with a lower risk of HCC development as compared to the non-antiplatelet group in most subgroups (Supplementary Table 8). However, the majority of subgroup analyses in HCC risk comparisons between non-antiplatelet and antiplatelet groups showed a significantly lower

risk of HCC development in the antiplatelet group. Although some comparison groups that did not show significant differences, probably due to small patient numbers in the subgroups, most adjusted HRs were below 1.00.

Subgroup Analyses According to Persistent Viremia

Of 1,498 patients in whom viral breakthrough did not occur, 16 patients had persistent detectable serum HBV DNA in the absence of viral breakthrough during antiviral therapy. The persistent detectable viremia was not associated with a risk of HCC development. The risk of HCC development in the 16 patients was comparable to that of those with persistent undetectable HBV DNA (n=911; HR: 4.24, 95% CI: 0.55–32.63, *P*=0.17) and to that of those with intermittent low-level viremia (n=571; HR: 1.97, 95% CI: 0.25–15.35, *P*=0.52).

Association between Bleeding Events and Antiplatelet Therapy

During the study period, 1.8% (20 of 1,116) patients in the non-antiplatelet group and 9.5% (53 of 558) in the antiplatelet group experienced bleeding events. The major event in both groups was upper gastrointestinal tract bleeding (Supplementary Table 9). The results of bleeding sources and major bleeding events were described in the Supplementary Document 6.

Overall, bleeding risk in the antiplatelet group was significantly higher than that in the non-antiplatelet group (HR: 3.28, 95% CI: 1.98–5.42, *P*<0.001). In a time-varying Cox regression analysis of the entire cohort, bleeding risk in patients treated with aspirin was not significantly different from risk in the non-antiplatelet group (HR: 1.11, 95% CI: 0.48–2.54, *P*=0.81). However, bleeding risk in patients treated with clopidogrel or dual antiplatelets was significantly higher than in the non-antiplatelet group, respectively: the clopidogrel group

(HR: 4.71, 95% CI: 1.81–12.22, *P*=0.001); the dual antiplatelet group (HR: 7.37, 95% CI: 4.20–12.92, *P*<0.001). The cumulative incidence rates of bleeding events at 5 years were 2.7% in the non-antiplatelet group and 2.6%, 12.6%, and 19.7% in aspirin, clopidogrel, and dual antiplatelets group, respectively (Fig. 3A).

Among 215 patients who received clopidogrel, 2 were also treated with omeprazole. Since it was well known that omeprazole decreases the effect of clopidogrel (19), we performed subgroup analyses after excluding those 2 patients taking both medications. In those subgroup analyses, risk of HCC development in patients treated with clopidogrel or dual antiplatelets were also not significantly different from those in the non-antiplatelet group: clopidogrel group (HR: 0.97, 95% CI: 0.24–3.99, *P*=0.97); dual antiplatelet group (HR: 0.97, 95% CI: 0.41–2.26, *P*=0.94).

In propensity score-matching analysis, bleeding risk in the antiplatelet group was not significantly higher than in the non-antiplatelet group again (HR: 2.06, 95% CI: 0.93–4.57, *P*=0.07). Bleeding risk in patients treated with aspirin or clopidogrel did not significantly differ from those not treated with antiplatelet therapy: aspirin (HR: 0.85, 95% CI: 0.31–2.29, *P*=0.75), and clopidogrel groups (HR: 2.81, 95% CI: 0.92–8.59, *P*=0.07). Bleeding risk in patients treated with dual antiplatelets was significantly higher than in the non-antiplatelet group (HR: 5.36, 95% CI: 2.27–12.66, *P*<0.001). In the propensity score-matched set, the cumulative incidence rates of bleeding events at 5 years were 2.7% in the non-antiplatelet group, and 2.1%, 9.6%, and 10.1% in aspirin, clopidogrel, and dual antiplatelets groups, respectively (Fig. 3B).

Competing risks analysis was performed for bleeding events in the entire cohort and the propensity score-matched cohort; liver transplantation was considered a competing event. After competing risk analysis, bleeding risk in the antiplatelet group was significantly higher

than in the non-antiplatelet group (HR: 3.75, 95% CI: 2.30–6.11, *P*<0.001 in the entire cohort; and HR: 2.28, 95% CI: 1.18–4.42, *P*=0.01 in the propensity score-matched cohort). Bleeding risk in patients treated with aspirin did not significantly differ from risk in the non-antiplatelet group (HR: 1.32, 95% CI: 0.60–2.90, *P*=0.48 in the entire cohort; HR: 0.54, 95% CI: 0.16–1.87, *P*=0.34 in the propensity score-matched cohort). However, bleeding risk in patients treated with clopidogrel or dual antiplatelets therapy was significantly higher than in the non-antiplatelet group in the entire cohort, respectively: clopidogrel (HR: 6.07, 95% CI: 2.65–13.90, *P*<0.001), and dual antiplatelet groups (HR: 8.27, 95% CI: 4.74–14.45, *P*<0.001). In the propensity score-matched cohort, bleeding risk in patients treated with clopidogrel was not significantly higher than in the non-antiplatelet group (HR: 3.24, 95% CI: 0.94–11.17, *P*=0.06). In patients with dual antiplatelets, bleeding risk was significantly higher than in the non-antiplatelet group (HR: 5.97, 95% CI: 2.90–12.31, *P*<0.001). Difference in bleeding-related deaths was not applicable between the antiplatelet and the non-antiplatelet groups (no death in the non-antiplatelet group and 2 deaths in the antiplatelet group) (Supplementary Document 6).

When the causes of antiplatelet therapy were considered for bleeding events, coronary heart disease, arrhythmia, and brain infarcts were found not to be independent predictors in this study (Supplementary Document 5). When adjusting for the three factors, bleeding risk in patients treated with dual antiplatelets, not with aspirin or clopidogrel, was significantly higher than in the non-antiplatelet group.

Association between Other Comorbidities and Antiplatelet Therapy

Fifty-six patients (3.4%) newly developed malignancies other than HCC and there was no significant difference during the study period: 2.6% (29 of 1,116) in the non-antiplatelet

group and 4.8% (27 of 558) in the antiplatelet group (Supplementary Table 10). The risk of malignancy other than HCC, end-stage kidney disease, and cardiovascular events, including myocardial infarction, was described in the Supplementary Document 7.

Discussion

This observational study showed that antiplatelet therapy is associated with a significantly lower risk of HCC development in CHB patients with controlled HBV DNA levels using antiviral treatment. Immortal time bias is often unrecognized in epidemiologic studies of drug effect on cancer development. To minimize immortal time bias for HCC development in this study, we used a time-varying Cox regression analysis. A time-varying Cox proportional hazards regression analysis is more accurate for defining antiplatelet exposure status than the conventional Cox proportional hazards analysis, because the analysis takes into account variations in the timing of antiplatelet initiation in patients and considers the period of non-exposure to antiplatelet agent (20). After immortal time bias was controlled for HCC development by this method, HCC incidence rates in the antiplatelet group showed significantly lower than those in the non-antiplatelet group. These results were observed consistently in several analyses, including a time-varying Cox proportional hazards model for the entire cohort, competing risks, and propensity score-matched analyses.

Antiplatelet therapy had additive effects on antiviral treatment for risk reduction of HCC development in this study. This result implies that underlying chronic inflammation in the liver is important in facilitating HCC development, as well as uncontrolled HBV DNA. In CHB patients, virus-induced $CD8^+$ lymphocytes produce inflammatory cytokines to cope with the infection, but they also damage the remaining liver tissue if the viral clearance is unsuccessful. This repeated damage to hepatocytes eventually results in developing cirrhosis and HCC (21, 22). During this microinflammation, platelets play a key role to accumulate $CD8^+$ T cells in the liver (23). Platelets also produce platelet-derived growth factor-β to activate hepatic stellate cells and promote fibrosis in animal model. Antiplatelet therapy will decrease platelet activation, decrease $CD8^+$ cells, and thus prevent HCC development (21),

and selectively inhibit platelet-derived growth factor-β to reduce biliary fibrosis in patients with liver disease (24).

Given that aspirin alone did not significantly increase the bleeding risk in all of time-varying Cox regression, propensity score-matched, and competing risk analyses compared to the non-antiplatelet group, aspirin use is a feasible option in preventing HCC development in CHB patients with controlled HBV DNA levels. Although dual antiplatelets group has shown the strongest preventive effects against HCC occurrence in preclinical studies, the clinical benefit of dual antiplatelet therapy in an actual clinical setting was not satisfactory, as bleeding risk in patients treated with dual antiplatelets was much higher than in those not treated with antiplatelets.

In the entire cohort, NAFLD was an independent risk factor for HCC development (HR: 2.93, 95% CI: 1.06–8.19, P=0.04). However, the proportion of patients with NAFLD in the antiplatelet group (30.3%, 169 of 558) was significantly higher than in the non-antiplatelet group (19.8%, 221 of 1,116, P<0.001). Notably, the risk of HCC development in the antiplatelet group was significantly lower than in the non-antiplatelet group, although the additional HCC risk attributed to NAFLD in the antiplatelet group may be higher than that in the non-antiplatelet group.

There are some limitations in this study. First, the current study was based on retrospective observational data. Thus, our findings are potentially subject to selection bias and confounding effects. There were several imbalanced factors between study groups. To overcome this limitation, an additional analysis using propensity score matching was performed. In this analysis, HCC incidence rates in the antiplatelet group were significantly lower than those in the non-antiplatelet group. Second, the sample size was not sufficient to perform several subgroup analyses. For example, among patients who experienced viral

breakthrough during follow-up period, we did not find a significant association between antiplatelet therapy and HCC risk reduction. The relatively small number of patients treated with antiplatelet (only 50 cases) did not allow for a comprehensive evaluation, particularly in patients who experienced viral breakthrough. Given that very low viral breakthrough rates of high potency antiviral drugs in this era, viral breakthrough might not be a major hurdle for chemopreventive effects of antiplatelets. In addition, although a tendency existed for a greater HCC development in patients with persistent detectable low-level viremia than in those with undetectable and intermittent low-level viremia, there was no significant difference in HCC development among the three groups in this study. This may be explained also by the small number of patients with persistent detectable low-level viremia (n=16) and the low incidence rates of HCC development due to a relatively low rate of cirrhosis (12.2%) compared to that in the original study (50.6%) (25). Third, several clinical data were not available due to retrospective nature of this study. A previous study showed that CHB patients with serum HBV DNA levels<2,000 IU/mL and HBsAg levels>1,000 IU/mL were associated with a significantly higher risk of HCC development (26). Furthermore, previous studies also demonstrated that HBV genotype, BCP mutations, pre-S deletion mutants, a family history of HCC, as well as metabolic syndrome were also important risk factors for HCC in CHB patients (27). Unfortunately, information about serum HBsAg levels, BCP mutations, pre-S deletion mutations, a family history of HCC, serum fasting glucose and insulin levels, and metabolic syndrome was not available for the majority of our patients due to the retrospective nature of our study, and therefore the possible risk of such factors for HCC development could not be evaluated in our study. In further studies, such pivotal factors should be considered in prospective studies of HCC risk assessments.

It was difficult to find out the treatment duration of antiplatelet therapy that determines the

risk of HCC development in this study. Although results suggested that antiplatelet therapy was significantly associated with a lower risk of HCC development (56% reduction) when the median duration of exposure to antiplatelet therapy was 27.6 months, it is unknown to clarify exactly how long patients should receive antiplatelet therapy to prevent HCC development. When HCC occurred during the early period of antiplatelet therapy, the effect of antiplatelet therapy on HCC development can be misinterpreted such that antiplatelet therapy increases the HCC risk (28, 29).

In conclusion, the present study in CHB patients with suppressed HBV DNA levels showed that antiplatelet therapy was associated with a significantly lower risk of HCC development. Additive treatment of aspirin in patients with durable viral suppression might be one of effective strategies to lower HCC development. Although antiplatelet therapy increased the bleeding risk in CHB patients, only aspirin use did not significantly increase the bleeding risk in contrast to increased bleeding risk in patients treated with clopidogrel or dual antiplatelets. Given the high fatality rates after HCC diagnosis, further large-scale studies are needed to confirm the chemopreventive effect of aspirin on HCC development, particularly in populations at high risk of HCC development under well control of prognostic factors. In addition, prospective studies using paired biopsies are needed to elucidate the mechanism of antiplatelet agents in the future: whether or not chemoprevention effects of antiplatelet agents on HCC development are caused by fibrosis reversal by antiplatelet agents.

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Author names in bold designate shared co-first authorship.

Figure Legends

Figure 1. Patient flow diagram.

Patients excluded when treated with other potential chemopreventive drugs such as stains, metformin, sulfonylurea, insulin, and NSAID, and with ≥2 above drugs.

[a]Concurrent drugs (n=1,748) of statins (n=309), metformin (n=243), sulfonylurea (n=109), insulin (n=103), NSAID (n=341), and ≥2 of above drugs (n=643) in the non-antiplatelet group

[b]Pegylated interferon-α (n=112), and clevudine (nucleoside analog)- (n=2,591) or tenofovir disoproxil fumarate (TDF)-containing regimens (n=4,032) were excluded in the non-antiplatelet group. None of the patients in the antiplatelet group were treated with pegylated interferon-α, or with a clevudine- or TDF-containing regimen.

[c]Concurrent drugs (n=691) of statins (n=132), metformin (n=91), sulfonylurea (n=34), insulin (n=37), NSAID (n=133), and ≥2 of above drugs (n=264) in the antiplatelet group

Abbreviations: HBsAg, surface antigen of the hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, Human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drugs; OTC, over-the-counter

Figure 2. Kaplan-Meier estimates of cumulative incidence of HCC in the entire cohort and propensity score-matched cohorts. Propensity score matching of the entire cohort created 420 matched pairs of patients. (A) Cumulative incidence of HCC in non-antiplatelet and antiplatelet groups in the entire cohort: non-antiplatelet group vs. antiplatelet group (P=0.04 by log-rank test). (B) Cumulative incidence of HCC according to antiplatelet drugs in the entire cohort: non-antiplatelet group vs. aspirin (P=0.02 by log-rank test), clopidogrel (P=0.98 by log-rank test), and dual antiplatelets groups (P=0.64 by log-rank test),

respectively. (C) Cumulative incidence of HCC in the non-antiplatelet and antiplatelet groups in the propensity score-matched cohorts: non-antiplatelet group vs. antiplatelet group (P=0.007 by log-rank test). (D) Cumulative incidence of HCC according to antiplatelet drugs in propensity score-matched cohorts: non-antiplatelet group vs. aspirin (P<0.001 by log-rank test), clopidogrel (P=0.02 by log-rank test), and dual antiplatelets groups (P=0.001 by log-rank test), respectively. (E) Cumulative incidence of HCC in the antiplatelet group according to PAGE-B score (P=0.007 by log-rank test). (F) Cumulative incidence of HCC in the non-antiplatelet group according to PAGE-B score (P<0.001 by log-rank test). Risk for HCC occurrence was stratified by PAGE-B score: low-risk, PAGE-B score <10: intermediate-risk, 10 ≤ PAGE-B score <18; and high-risk, PAGE-B score ≥18.

*Dual antiplatelet therapy means a combination therapy of aspirin and clopidogrel.

Abbreviations: AP, antiplatelet.

Figure 3. Kaplan-Meier estimates of cumulative incidence of bleeding events in the entire cohort and propensity score-matched cohorts. (A) Cumulative incidence of bleeding events according to antiplatelet drugs in the entire cohort: non-antiplatelet group vs. aspirin (P=0.80 by log-rank test), clopidogrel (P=0.001 by log-rank test), and dual antiplatelets group (P<0.001 by log-rank test), respectively. (B) Cumulative incidence of bleeding events according to antiplatelet drugs in the propensity score-matched cohorts: non-antiplatelet group vs. aspirin (P=0.76 by log-rank test), clopidogrel (P=0.05 by log-rank test), and dual antiplatelets group (P<0.001 by log-rank test), respectively.

*Dual antiplatelet therapy means a combination therapy of aspirin and clopidogrel.

Abbreviations: AP, antiplatelet.

Tables

Table 1. Baseline Characteristics

	Non-antiplatelet group (n=1,116)	Antiplatelet group				*P* value[b] (Non-AP vs AP)	*P* value[c] (Non-AP vs A vs C vs D)
		All (n=558)	Aspirin (n=343)	Clopidogrel (n=90)	Dual[a] (n=125)		
Age (years)	50.3 ± 10.8	55.2 ± 11.0	54.2 ± 11.1	57.3 ± 11.5	56.5 ± 10.0	<0.001	<0.001
Male, N (%)	716 (64.2%)	339 (60.8%)	197 (57.4%)	57 (63.3%)	85 (68.0%)	0.09	0.17
DM, N (%)	93 (8.3%)	184 (33.0%)	125 (36.4%)	24 (26.7%)	35 (28.0%)	<0.001	<0.001
Cirrhosis, N (%)	136 (12.2%)	68 (12.2%)	42 (12.2%)	13 (14.4%)	13 (10.4%)	1.000	0.85
Cause of antiplatelet therapy, N (%)						<0.001	<0.001
Preventive		235 (42.1%)	195 (56.9%)	18 (20.0%)	22 (17.6%)		
Coronary heart disease		169 (30.3%)	66 (19.2%)	29 (32.2%)	74 (59.2%)		
Arrhythmia		41 (7.3%)	31 (9.0%)	4 (4.4%)	6 (4.8%)		
Brain infarct		40 (7.2%)	11 (3.2%)	19 (21.1%)	10 (8.0%)		

Others[c]		73 (13.1%)	40 (11.7%)	20 (22.2%)	13 (10.4%)		
CTP class						<0.001	<0.001
A	1,095 (99.1%)	514 (92.1%)	309 (90.1%)	87 (96.7%)	118 (94.4%)		
B	21 (1.9%)	44 (7.6%)	34 (9.9%)	3 (3.3%)	7 (5.6%)		
C	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
MELD score	8.1 ± 2.9	9.1 ± 3.7	8.9 ± 3.5	9.8 ± 4.5	9.2 ± 3.5	<0.001	<0.001
HBeAg positivity, N (%)	272 (24.4%)	81 (14.5%)	55 (16.0%)	4 (4.4%)	22 (17.6%)	<0.001	<0.001
HBV DNA (log_{10} IU/mL)	1.5 ± 0.6	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	1.3 ± 0.6	0.03	0.01
ALT (IU/L)						<0.001	<0.001
< 80	1,044 (93.5%)	514 (92.1%)	311 (90.7%)	85 (94.4%)	118 (94.4%)		
80–200	72 (6.5%)	30 (5.4%)	22 (6.4%)	4 (4.4%)	4 (3.2%)		
> 200	0 (0.0%)	12 (2.2%)	8 (2.3%)	1 (1.1%)	3 (2.4%)		
Albumin (g/dL)	4.3 [4.1, 4.5]	4.2 [3.8, 4.4]	4.2 [3.8, 4.4]	4.3 [3.8, 4.5]	4.1 [3.7, 4.4]	<0.001	<0.001
Total bilirubin (mg/dL)	0.8 [0.6, 1.1]	0.9 [0.6, 1.2]	0.9 [0.7, 1.1]	0.8 [0.6, 1.2]	0.8 [0.6, 1.2]	0.16	0.09
Creatinine (mg/dL)	0.9 [0.8, 1.0]	1.0 [0.8, 1.1]	0.9 [0.8, 1.1]	1.0 [0.9, 1.1]	1.0 [0.9, 1.1]	<0.001	<0.001

PT INR	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.77	0.77
Platelet ($\times 10^3$ /μL)	194 [169, 229]	191 [146, 234]	195 [151, 238]	184 [127, 224]	184 [150, 226]	<0.001	<0.001

Values are expressed as the median with interquartile range (IQR) for continuous variables and frequency with proportion for categorical variables.

Abbreviations: A, aspirin group; AP, antiplatelet group; C, clopidogrel group; CTP, Child-Turcotte-Pugh; D, dual therapy group; DM, diabetes mellitus; HBeAg, hepatitis B virus e antigen; MELD, model for end-stage liver disease; non-AP, non-antiplatelet group; PT INR, international normalized ratio for prothrombin time; y, years.

[a]Dual antiplatelet therapy means a combination treatment of aspirin and clopidogrel.

[b]*P* value as comparison of the antiplatelet and non-antiplatelet groups; [c]*P* value as comparison of the non-antiplatelet, aspirin, clopidogrel, and dual therapy groups

P value estimated by χ^2-test or Fisher's exact test for categorical variables, and Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables.

[c]Other causes included peripheral vessel disease, transient ischemic attack, small vessel disease in the brain, valvular heart disease, cardiomyopathy, and brain aneurysm coiling.

Table 2. Time-varying Cox Proportional Hazards Regression Analysis for HCC Development in the Entire Cohort

	Univariable		Multivariable	
	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[a]
Age (years)	1.04 (1.02, 1.07)	0.001	1.04 (1.01, 1.06)	0.002
Male, N (%)	1.54 (0.88, 2.69)	0.13		
DM, N (%)	1.08 (0.59, 1.99)	0.81		
Cirrhosis, N (%)	2.48 (1.40, 4.40)	0.002	0.97 (0.49, 1.92)	0.93
CTP class				
B vs. A (reference)	1.75 (0.57, 4.08)	0.26		
C vs. A (reference)	9.84 (0.08, 68.52)	0.11		
HBeAg positivity, N (%)	0.98 (0.54, 1.78)	0.95		
HBV DNA (log_{10} IU/mL)	0.73 (0.48, 1.12)	0.15		
ALT (IU/L)				
80–200 vs. < 80	0.87 (0.24, 2.21)	0.80		
> 200 vs. < 80	0.61 (0.01, 4.22)	0.73		
Albumin (g/dL)	0.60 (0.39, 0.93)	0.02	0.68 (0.40, 1.15)	0.15
Total bilirubin (mg/dL)	0.97 (0.71, 1.33)	0.84		
Creatinine (mg/dL)	0.90 (0.66, 1.23)	0.51		
PT INR	2.97 (1.22, 7.19)	0.02	1.81 (0.56, 5.78)	0.32
Platelet ($\times 10^3$ /μL)	0.990 (0.986 0.995)	<0.001	0.991 (0.985, 0.997)	0.002
Viral breakthrough	2.10 (1.19, 3.73)	0.01	2.46 (1.36, 4.46)	0.003
Antiplatelet therapy, N (%)	0.58 (0.31, 0.86)	0.04	0.44 (0.23, 0.85)	0.01
Aspirin	0.33 (0.12, 0.91)	0.03	0.26 (0.09, 0.74)	0.01

Clopidogrel	0.97 (0.24, 3.99)	0.97	0.63 (0.15, 2.65)	0.53
Dual antiplatelets[b]	0.96 (0.41, 2.23)	0.91	0.67 (0.28, 1.60)	0.37

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; HBeAg, hepatitis B virus e antigen; HR, hazards ratios; MELD, model for end-stage liver disease; PT INR, international normalized ratio for prothrombin time; y, years.

[a]*P* value estimated by Cox proportional hazard regression with Firth's penalized likelihood.

[b]Dual antiplatelets mean a combination treatment of aspirin and clopidogrel.

Table 3. Characteristics of Propensity Score-matched Cohorts

	Non-antiplatelet group (n=420)	Antiplatelet group (n=420)	*P* value[a]
Age (years)	54.7 ± 10.5	54.5 ± 11.1	0.69
Male, N (%)	258 (61.4%)	259 (61.7%)	0.94
DM, N (%)	82 (19.5%)	85 (20.2%)	0.71
Cirrhosis, N (%)	34 (8.1%)	43 (10.2%)	0.25
CTP score	5.2 ± 0.6	5.2 ± 0.5	0.85
MELD score	8.6 ± 4.0	8.6 ± 3.0	0.94
HBeAg positivity (%)	68 (16.2%)	65 (15.5%)	0.75
ALT (IU/L)	28 [18, 48]	27 [19, 39]	0.71
Albumin (g/dL)	4.2 [4.0, 4.4]	4.2 [3.9, 4.5]	0.93
Total bilirubin (mg/dL)	0.8 [0.6, 1.1]	0.9 [0.6, 1.1]	0.68
Creatinine (mg/dL)	0.9 [0.7, 1.0]	1.0 [0.8, 1.1]	0.92
PT INR	1.0 [1.0, 1.1]	1.0 [1.0, 1.1]	0.73
Platelet ($\times 10^3/\mu L$)	189 [165, 220]	196 [156, 239]	0.56
Viral breakthrough	44 (10.5%)	41 (9.8%)	0.74

Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; HBeAg, hepatitis B virus e antigen; HR, hazards ratios; MELD, model for end-stage liver disease; PT INR, international normalized ratio for prothrombin time; y, years.

[a]*P* value estimated by paired t-test for continuous variables and McNemar test for categorical variables.

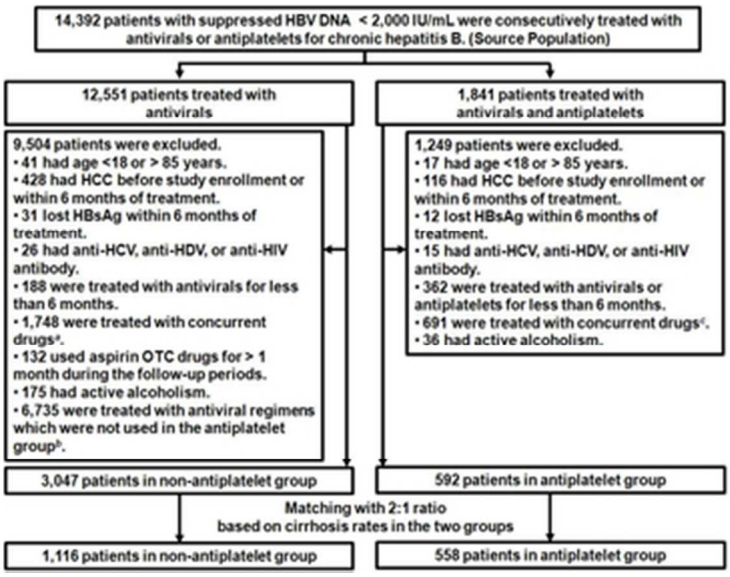

Figure 1. Patient flow diagram.
Patients excluded when treated with other potential chemopreventive drugs such as stains, metformin, sulfonylurea, insulin, and NSAID, and with ≥2 above drugs.
aConcurrent drugs (n=1,748) of statins (n=309), metformin (n=243), sulfonylurea (n=109), insulin (n=103), NSAID (n=341), and ≥2 of above drugs (n=643) in the non-antiplatelet group
bPegylated interferon-α (n=112), and clevudine (nucleoside analog)- (n=2,591) or tenofovir disoproxil fumarate (TDF)-containing regimens (n=4,032) were excluded in the non-antiplatelet group. None of the patients in the antiplatelet group were treated with pegylated interferon-α, or with a clevudine- or TDF-containing regimen.
cConcurrent drugs (n=691) of statins (n=132), metformin (n=91), sulfonylurea (n=34), insulin (n=37), NSAID (n=133), and ≥2 of above drugs (n=264) in the antiplatelet group
Abbreviations: HBsAg, surface antigen of the hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, Human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drugs; OTC, over-the-counter

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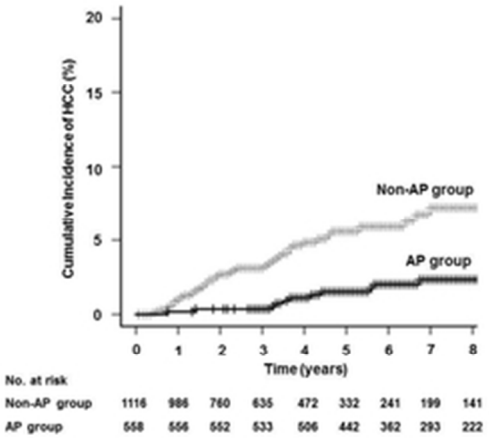

Figure 2. Kaplan-Meier estimates of cumulative incidence of HCC in the entire cohort and propensity score-matched cohorts. Propensity score matching of the entire cohort created 420 matched pairs of patients. (A) Cumulative incidence of HCC in non-antiplatelet and antiplatelet groups in the entire cohort: non-antiplatelet group vs. antiplatelet group (P=0.04 by log-rank test). (B) Cumulative incidence of HCC according to antiplatelet drugs in the entire cohort: non-antiplatelet group vs. aspirin (P=0.02 by log-rank test), clopidogrel (P=0.98 by log-rank test), and dual antiplatelets groups (P=0.64 by log-rank test), respectively. (C) Cumulative incidence of HCC in the non-antiplatelet and antiplatelet groups in the propensity score-matched cohorts: non-antiplatelet group vs. antiplatelet group (P=0.007 by log-rank test). (D) Cumulative incidence of HCC according to antiplatelet drugs in propensity score-matched cohorts: non-antiplatelet group vs. aspirin (P<0.001 by log-rank test), clopidogrel (P=0.02 by log-rank test), and dual antiplatelets groups (P=0.001 by log-rank test), respectively. (E) Cumulative incidence of HCC in the antiplatelet group according to PAGE-B score (P=0.007 by log-rank test). (F) Cumulative incidence of HCC in the non-antiplatelet group according to PAGE-B score (P<0.001 by log-rank test). Risk for HCC occurrence was stratified by PAGE-B score: low-risk, PAGE-B score <10: intermediate-risk, 10 ≤ PAGE-B score <18; and high-risk, PAGE-B score ≥18.
*Dual antiplatelet therapy means a combination therapy of aspirin and clopidogrel.
Abbreviations: AP, antiplatelet.

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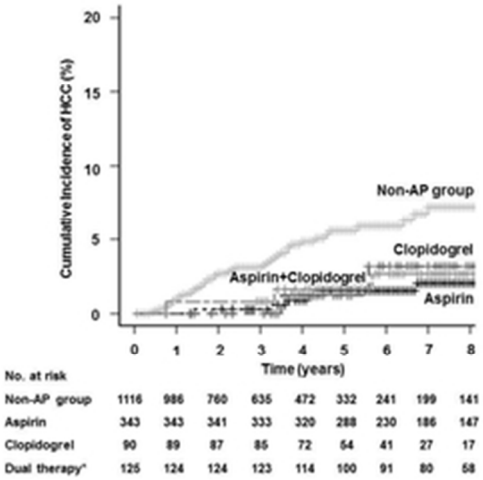

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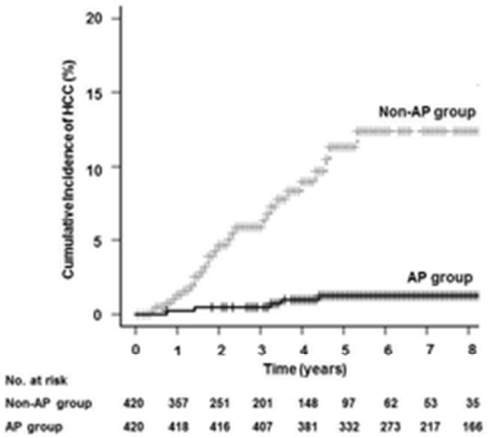

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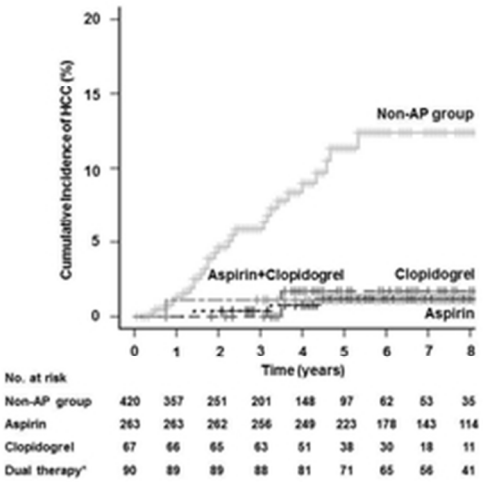

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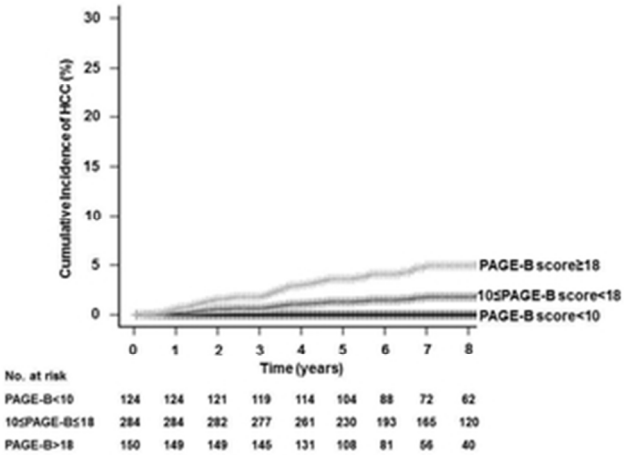

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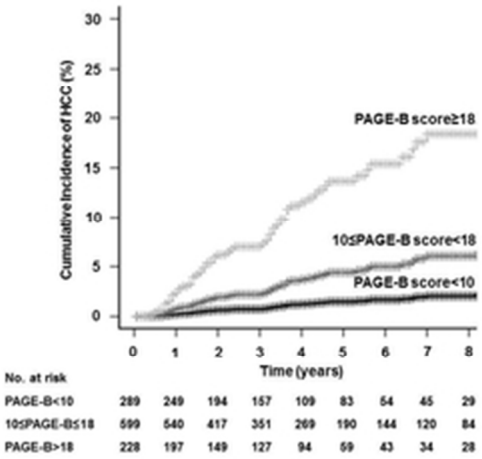

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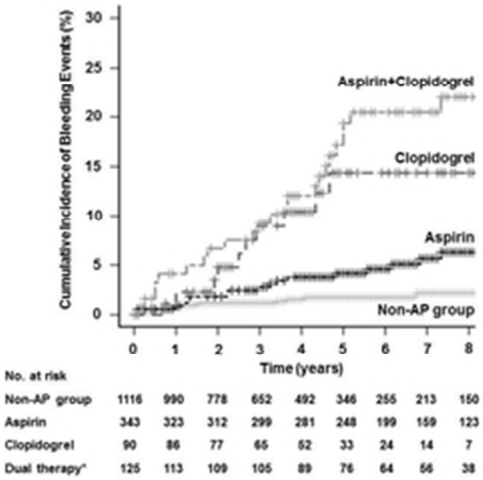

Figure 3. Kaplan-Meier estimates of cumulative incidence of bleeding events in the entire cohort and propensity score-matched cohorts. (A) Cumulative incidence of bleeding events according to antiplatelet drugs in the entire cohort. (B) Cumulative incidence of bleeding events according to antiplatelet drugs in the propensity score-matched cohorts.
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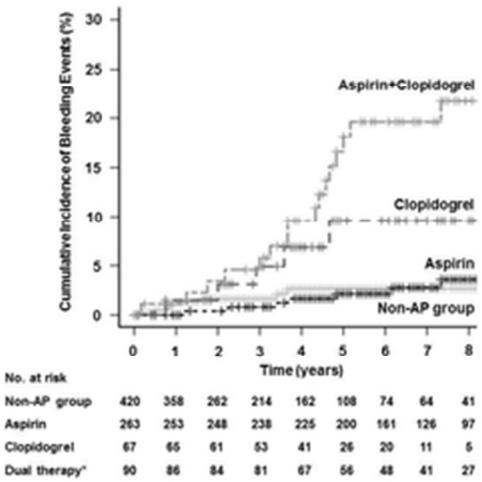

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