Nucleos(t)ide analogue continuous therapy associated with reduced adverse outcomes of chronic hepatitis B

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Abstract

Background: Nucleos(t)ide analogue (NA) therapy reduces the risk of disease progression in chronic hepatitis B virus-infected patients. However, the risk of liver decompensation, hepatic failure, and mortality after discontinuation of NA therapy remains unknown.

Methods: Among 51,574 chronic hepatitis B patients who received NAs in the Taiwan National Health Insurance Research Database, we identified 8,631 patients who continued NA therapy (treatment cohort) and 8,631 propensity-score matched patients who stopped NA therapy after their initial 1.5 years treatment (off-therapy cohort) between October 1, 2003 and December 31, 2011. All study subjects were followed up from the index date, that is, the date 1.5 years after the first prescription of NA, until development of liver decompensation and hepatic failure, death or end of 18-month follow-up period.

Results: Treatment cohort had significantly lower risks of liver decompensation (1.05%; 95% confidence interval [CI], 0.81%–1.30% vs 2.13%; 95% CI, 1.82%–2.45%; $p < 0.001$), hepatic failure (0.35%; 95% CI, 0.21%–0.49% vs 0.63%; 95% CI, 0.46%–0.80%; $p = 0.008$) and overall mortality (1.67%; 1.37%–1.98% vs 2.44%; 95% CI, 2.10%–2.77%; $p < 0.001$) during the 18-month follow-up period. After adjusting for potential confounders, NA continuous therapy was associated with reduced risks of liver decompensation (hazard ratio [HR]: 0.47; 95% CI, 0.36–0.62, $p < 0.001$), hepatic failure (HR: 0.53; 95% CI, 0.33–0.86, $p = 0.01$) and overall mortality (HR: 0.67; 95% CI, 0.53–0.84, $p = 0.001$). The number needed to reduce one less disease progression and mortality was 47. The protective effect of NA continuous therapy was found in nearly all subgroups.

Conclusion: NA continuous therapy is associated with reduced risks of liver decompensation, hepatic failure, and overall mortality.

Keywords: Antiviral therapy; Hepatic failure; Hepatitis B; Liver decompensation; Mortality

1. INTRODUCTION

Chronic hepatitis B infection (CHB) is a major health issue worldwide because of its global distribution and risks of adverse outcomes including liver cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC).[1,2] Active viral replication is associated with continuing liver damage and decreased survival over time. Hepatitis B virus (HBV) replication has been identified as a major element of immune-mediated liver tissue injury and disease progression.[3] Higher serum HBV DNA levels are associated with an increased risk of HCC development and postoperative recurrence.[3–5]

Nucleos(t)ide analogue (NA) therapy effectively suppresses HBV replication.[6] NA therapy delays the disease progression in CHB patients, leads to regression of liver cirrhosis, and it reduces the risk of HCC development.[7–10] Recently, we reported a reduced risk of HCC in patients receiving NA therapy based on a nationwide cohort.[11] Treating CHB patients at a younger age, in the non-cirrhotic stage and in the absence of liver decompensation, is associated with better effects including secondary HCC prevention.[11] In addition, we found an association between NA therapy and decreased postoperative HCC recurrence,[12] and that the tertiary preventive effects of NAs are more obvious in HCC patients at earlier stages.[5]

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Because a high HBV viral load and associated hepatic inflammation are the main drivers of liver damage, effective and sustained suppression of viral replication and hepatic inflammation through NA therapy are the key elements in stopping the progression to liver fibrosis, cirrhosis, and liver failure.[8,13,14] However, when to stop NA therapy and how severe the disease will progress after NA discontinuation remains controversial.[15–18] It is well known that NA therapy cessation leads to virological and clinical relapse, both in patients with positive and those with negative hepatitis B e antigen (HBeAg) in their serum.[17,19] However, the more important clinical major outcomes, such as liver decompensation, hepatic failure, and overall mortality after discontinuation of NA therapy, are seldom reported.[20] In the present study, we aimed to compare the long-term outcomes between patients with continuous NA therapy and those after cession of NA treatment based on a nationwide cohort. We also examined this association among different subgroups and calculated the number needed to be treated (NNT) for one less disease progression.

2. METHODS

2.1. Study population and study design

Based on data from Taiwan's National Health Insurance Research Database (NHIRD), we conducted a retrospective cohort study. Constructive health information, such as patient diagnoses, prescriptions, and laboratory check-up items, is available from the NHIRD, which we have described in previous studies.[11] International classification of diseases-9 (ICD-9) codes are used to define diseases in this database. This study was approved by the ethics review board of Taiwan's National Health Research Institutes.

We defined CHB NA users according to the following two criteria: (1) CHB (ICD-9 codes: 070.2, 070.3, and V02.61) diagnosed three times in an outpatient clinic or once during hospitalization between October 1, 2003 and December 31, 2011; and (2) NA use for at least 90 days. The NAs in the present study included lamivudine, adefovir, entecavir, telbivudine, and tenofovir. NAs have been covered under Taiwan's National Health Insurance (NHI) program for CHB patients since October 1, 2003. Initially, the approved duration of antiviral treatment was only 18 months. In 2009, the treatment duration was extended to 36 months for CHB patients and to lifelong for cirrhotic patients. Detailed NHI reimbursement criteria have been described in our previous studies.[5,11,12] Consequently, this NHI policy change offered an excellent opportunity to compare the beneficial effect of continuous NA therapy in the extended 18 months after the initial 18 months NA treatment.

2.2. Study cohorts

Among the eligible patients having received NA therapy for at least 90 days, we first excluded those with hepatitis C virus (HCV) (ICD-9 codes: 070.41, 070.44, 070.51, 070.54, and V02.62), human immunodeficiency virus (HIV) (ICD-9 code: 042), other types of viral hepatitis (ICD-9 code: V02.69), and malignant tumors (ICD-9 codes: 104-208). Those with liver decompensation or a history of hepatic failure were also excluded. To avoid imbalanced bias resulting from immortal time bias, only those surviving the disease for at least 1.5 years from the start date of NA therapy were included in the analysis. All identified subjects were followed up from the index date, that is, the date 1.5 years after the first prescription of NAs, until development of major CHB complication, such as liver decompensation or hepatic failure, death, or end of the follow-up period on December 31, 2011. We defined the study subjects in the treatment cohort as those continuing NAs treatment after the index date. Those who did not use NAs after the index date were defined as off-therapy cohort.

Propensity scores were calculated using the logistic regression model to estimate the probabilities of NA continuous therapy and NA off-therapy. Age, gender, comorbidities, and concomitant drug use were analyzed in the calculation of the propensity scores. The propensity score estimation methods were performed as previously described.[11,21] We matched each patient in the treatment cohort with one patient in the off-therapy cohort, based on propensity scores. Histograms before and after propensity score matching were plotted to examine whether the patients enrolled into the two groups are comparable.

Comorbidities were designated by ICD-9 codes and included diabetes mellitus (250), hyperlipidemia (272.0-272.2), hypertension (401–405), acute coronary syndrome (410–414), cerebrovascular accident (430–438), chronic obstructive pulmonary disease (490–496), peptic ulcer disease (531–534), liver cirrhosis (571.5), and renal failure (584–586). Certain drugs, including non-steroidal anti-inflammatory drugs and metformin, which have been reported to attenuate the risk of CHB progression were also included in the propensity score estimation. We defined drug users as those taking more than one tablet per month during the follow-up period.

2.3. Main outcome measurements

Indicators of CHB progression, such as liver decompensation, hepatic failure, and death after the index dates, were defined as the main outcomes. Liver decompensation was defined if NA users were admitted or enrolled in the Registry for Catastrophic Illness Patient Database (RCIPD) with one of the following diagnoses: ascites (ICD-9 code: 789.5), hepatic encephalopathy (ICD-9 code: 572.2), portal hypertension (ICD-9 code: 572.3), hepatorenal syndrome (ICD-9 code: 572.4), or esophageal or gastric varices (ICD-9 codes: 456.0, 456.1, 456.2, and 456.8). RCIPD is a subset of the NHIRD. Patients are registered in the RCIPD only if their diagnoses are confirmed by laboratory data, image presentations, or pathological reports. Those who received gastric or esophageal variceal ligation or sclerotherapy were also defined as having liver decompensation. The first date of admission or date of enrollment in the RCIPD was defined as the date of liver decompensation development. Hepatic failure was defined if patients were admitted or enrolled in the Registry for Catastrophic Illness Patient Database with a diagnosis of hepatic failure (ICD-9 code: 570) or received liver transplantation. Death was defined if patients withdrew from the compulsory NHI program.

Cumulative incidences of the liver decompensation and hepatic failure were analyzed after controlling for competing mortality. Death may result from previous comorbidities, which may impact the risks of liver decompensation and hepatic failure. Death before liver decompensation or hepatic failure leads to informative censoring in estimating event incidences. Therefore, death before liver decompensation or hepatic failure should be considered to be a competing risk and adjusted. Death-adjusted cumulative incidences were analyzed using modified Kaplan-Meier method and the Gray method.[11] The R package "cmprsk" (http://cran.r-project.org/web/packages/cmprsk/index.html) was used to conduct competing risk analyses. The log-rank test was used to examine differences between the two groups. NNT was calculated by the inverse of the absolute risk reduction. NNT represented the number of patients that needed to be treated for one less disease progression.

2.4. Statistical analysis

To determine whether continuous NA therapy is independently associated with a reduced risk of CHB progression, we conducted multivariable analyses. In calculating the risks of liver

decompensation and hepatic failure, we used the Cox proportional hazards model that was adjusted for competing mortality and other potential confounders, including age, gender, and comorbidities. All parameters in the present study were defined *a priori* to exclude as many confounders as possible. Multivariable stratified analyses were conducted to examine the associations of NA off-therapy and the risk of CHB progression.

The demographic characteristics of the treatment cohort and off-therapy cohorts were compared using the χ^2 test and Student *t*-test. Cumulative incidences were analyzed using the survival and EpiTools packages of R program. All data management was performed with SAS 9.2 software (SAS Institute, Cary, NC) and a two-sided *p* value of <0.05 was considered statistically significant.

3. RESULTS

3.1. Demographic data

Between October 1, 2003 and December 31, 2011, 51,574 patients received NAs. Among them, 19,057 patients were excluded because they had <90 days of use or liver decompensation or hepatic failure before the index date. We excluded another 10,502 patients with malignancies, HCV, other types of viral hepatitis, or HIV before the index date, or with a follow-up period of <1.5 years after the start of NA therapy (Supplementary Fig. 1).

Among the remaining 22,069 patients, 11,261 patients who continued NA therapy after the initial 1.5 years of NA treatment were defined as the treatment cohort and 10,808 who did not receive NAs after the initial 1.5 years of treatment were defined as the off-therapy cohort. Becasue there were significant differences in demographic data (Supplementary Table 1) between the treatment cohort and the off-therapy cohort, we used propensity scores to estimate the probabilities of NA continuous therapy and NA off-therapy. The treatment cohort had a significantly higher propensity score (mean = 0.54) than the off-therapy cohort (mean = 0.48) ($p < 0.001$). The calculated propensity scores were used to match one patient in the treatment cohort with one patient in the off-therapy cohort. The histograms of the propensity scores before and after matching are shown in Supplementary Figure 2. Finally, we enrolled 8,631 patients in the treatment cohort and 8,631 patients in the off-therapy cohort.

These two matched cohorts were comparable in terms of demographic characteristics (Table 1). The mean age of the two groups was 40.6 years. Approximately, three-fourths of the patients were males. The median NAs therapy durations (since the initial NA prescription) for the off-therapy cohort and treatment cohort were 1.28 and 2.12 years, respectively. The median observation period was 18 months for both groups, from the index date (1.5 years after the first NAs prescription) to 3 years after the first NAs prescription. Compared with the off-therapy cohort, the treatment cohort had a significantly lower risk of liver decompensation, hepatic failure, and overall mortality (all $p < 0.001$).

3.2. Cumulative incidences of outcomes

After adjusting for competing mortality, the treatment cohort had a significantly lower risk of liver decompensation (Fig. 1A, $p < 0.001$), and hepatic failure (Fig. 1B, $p = 0.008$) compared with the off-therapy cohort. On average, the annual incidence of liver decompensation for treatment cohort and the off-therapy cohort were 0.70% and 1.42%, respectively. Additionally, the annual incidence of hepatic failure for the treatment cohort and the off-therapy cohort were 0.23% and 0.42%, respectively.

In Figure 1C, the cumulative incidence of overall mortality was significantly lower for the treatment cohort than for the off-therapy cohort ($p < 0.001$). On average, the annual overall mortality rate for the treatment cohort and the off-therapy cohort was 1.11% and 1.63%, respectively.

The cumulative incidence of composite disease progression outcome, that is, liver decompensation, hepatic failure, or overall mortality was 3.07% (95% confidence interval [CI], 2.73–3.46%) and 5.20% (95% CI, 4.75–5.69%) for the treatment cohort and the off-therapy cohort, respectively. The NNT that was associated with one less disease progression within 18 months was 47 (95% CI, 37–65). This suggests that NA continuous therapy in 47 patients is associated with one less disease progression to liver decompensation, hepatic failure, or mortality within 18 months.

3.3. Multivariable analysis

After adjusting for other confounders and competing mortality, we found that the treatment cohort was associated with a significantly lower risk of liver decompensation (hazard ratio [HR] = 0.47; 95% CI, 0.36–0.62, $p < 0.001$). Older age, male gender, liver cirrhosis, diabetes, and renal failure were also risk factors for liver decompensation (Table 2). Treatment cohort was an independent protective factor for hepatic failure after controlling for other potential confounders and competing mortality (HR = 0.53; 95% CI, 0.33–0.86, $p = 0.010$) (Table 3). In addition, the treatment cohort had a significantly lower risk of overall mortality compared with the off-treatment cohort after controlling for other confounders (HR = 0.67; 95% CI, 0.53–0.84, $p = 0.001$). Older age and liver cirrhosis were also risk factors for overall mortality in these CHB patients (Table 4).

In Figure 2, we conducted multivariable subgroup analyses. We found that the treatment cohort was associated with a reduced risk of CHB disease progression and overall mortality in nearly all subgroups compared with the off-treatment cohort, although some of the associations between the subgroups were not statistically significant because of the small event case numbers.

4. DISCUSSION

In this population-based study, we found that continuous NA therapy in CHB patients was associated with a significantly lower risk of liver decompensation, hepatic failure, and overall mortality. Continuous NA therapy in 47 patients was associated with one less disease progression to liver decompensation, hepatic failure, or mortality within 18 months. Several strengths of the present study may allow for broader generalization of our observations. First, this nationwide population-based study avoided potential selection bias, which is a major concern in clinical trials and observational studies. Second, compared with previous studies that were focused on clinical and virological relapses after NA discontinuation, this nationwide cohort study focused on more important outcomes, including liver decompensation, hepatic failure, and overall mortality. Third, we adjusted for competing mortality in analyzing the risks of liver decompensation and hepatic failure to provide an accurate estimation. Finally, a large sample size and comprehensive health information allowed us to match all potential confounders and conduct subgroups analyses to confirm our observations.

We have previously reported that NA therapy is associated with a reduced incidence of HCC for patients with CHB based on a nationwide cohort.[11] Because a high HBV viral load and associated hepatic inflammation are the main drivers of cirrhosis, liver decompensation, HCC development and post-operative HCC recurrence, effective and sustained suppression of viral replication, and hepatic inflammation are the key elements to

Table 1

Baseline demographic characteristics and outcomes of study cohorts

	Treatment Cohort[a] (N = 8,631) Number (%)	Off-therapy Cohort[a] (N = 8,631) Number (%)	p*
Age (mean ± SD)	40.6 ± 12.9	40.6 ± 12.94	0.933
Gender			0.388
Females	2311 (26.8)	2260 (26.2)	
Males	6320 (73.2)	6371 (73.8)	
Follow-up years (mean ± SD)[b]			
Mean±SD	2.72 ± 0.41	2.89 ± 0.31	<0.001
Median (IQR)	3.0 (2.41–3.0)	3.0 (3.0–3.0)	<0.001
NA therapy duration (years)[c]			
Mean ± SD	2.20 ± 0.53	1.13 ± 0.36	<0.001
Median (IQR)	2.12 (1.69–2.71)	1.28 (0.9–1.45)	<0.001
Concomitant drug users[d]			
NSAIDs or Aspirin	6358 (73.7)	6346 (73.5)	0.849
Metformin	565 (6.5)	618 (7.2)	0.117
Major coexisting diseases			
Acute coronary syndrome	189 (2.2)	156 (1.8)	0.082
Cerebral vascular disease	127 (1.5)	104 (1.2)	0.145
Chronic obstructive pulmonary disease	138 (1.6)	116 (1.3)	0.184
Diabetes	385 (4.5)	397 (4.6)	0.687
Cirrhosis	341 (4.0)	317 (3.7)	0.361
Renal failure	131 (1.5)	117 (1.4)	0.406
Hypertension	616 (7.1)	532 (6.2)	0.011
Hypercholesterolemia	55 (0.6)	51 (0.6)	0.770
Peptic ulcer diseases	627 (7.3)	604 (7.0)	0.515
Propensity Score[e]			
Mean±SD	0.51 ± 0.11	0.51±0.11	0.915
Median (IQR)	0.5 (0.44-0.58)	0.5 (0.44-0.58)	0.913
Events			
Liver decompensation	73 (0.8)	175 (2.0)	<0.001
Death before liver decompensation	89 (1.0)	141 (1.6)	
Hepatic failure	25 (0.3)	52 (0.6)	<0.001
Death before hepatic failure	117 (1.4)	196 (2.3)	
Overall death	119 (1.4)	200 (2.3)	<0.001

*Treatment cohort: continuing NAs therapy after their initial 1.5 years NAs treatment; Off-therapy cohort: not receiving NAs therapy after their initial 1.5 years NAs treatment.

*p values were compared using the χ^2 test and Student's t-test.

[b]Follow-up period starting from the index date, the date 1.5 years after the first NA prescription until liver decompensation, hepatic failure, or death.

[c]NA therapy duration calculated from the first prescription of NA.

[d]Drug users indicate patients using drugs at least one day per month on average.

[e]Age, gender, acute coronary syndrome, cerebral vascular diseases, chronic obstructive pulmonary disease, diabetes, cirrhosis, liver decompensation, renal failure, hypertension, hypercholesterolemia, use of statins, use of NSAIDs or aspirin or COXIBs, and use of metformin were included in the propensity score calculation.

IQR = interquartile range; N = number; NAs = nucleos(t)ide analogues; NSAIDs = non-steroidal anti-inflammatory drugs; SD = standard deviation.

halting disease progression.[5–7,14,22,23] However, when to stop NA therapy is a controversial medical and economic issue. Finite therapy is suggested for HBeAg-positive CHB patients when HBeAg seroconversion and consolidative therapy of 12- months duration are achieved.[15,24] A long-term, indefinite period of NA treatment may be needed for those who fail to achieve HBeAg seroconversion or HBeAg-negative CHB because of a high off-therapy hepatitis relapse rate and potential liver decompensation.[17,20,25,26] However, the beneficial effects of extended treatment on long-term CHB adverse outcomes have rarely been reported. In 2003, Taiwan initiated reimbursement for NAs therapy for CHB patients. However, the initial reimbursed duration was only 18 months because of drug resistance to lamivudine, which was the only NA available at that time. NAs reimbursement policy revisions were implemented in 2009 using serum HBV loads and ALT levels as guidelines for reimbursement, adding on adefovir therapy for lamivudine resistance, and providing strong potency with high genetic barrier. These include the extension of the duration of reimbursement to 36 months for CHB patients and to lifelong for cirrhotic patients. We, therefore, had a unique opportunity to compare the effects of different periods of NA treatment policy on the outcomes in CHB patients.

HBeAg-positive CHB patients are generally recommended to receive an additional 12 months of NAs therapy after HBeAg seroconversion to assure long-term durability and reduction in hepatitis flares.[15] However, there is still a high relapse rate even after at least 12 months of consolidation therapy following HBeAg seroconversion.[25,27,28] Reijnders et al.[25] reported that most CHB patients with HBeAg seroconversion that is induced by NAs do not have a durable response. In their study, only 22% of patients who discontinued NA treatment maintained a durable response, irrespective of the NAs that was used. Tseng et al.[29] and colleagues further demonstrated that for patients who achieved HBeAg seroconversion after NA therapy, they had a significantly higher risk of HBeAg sero-reversion and HBV reactivation than the spontaneous HBeAg seroconverters without antiviral therapy, especially in the young CHB patients. Thus, the recent updated clinical practice on the management

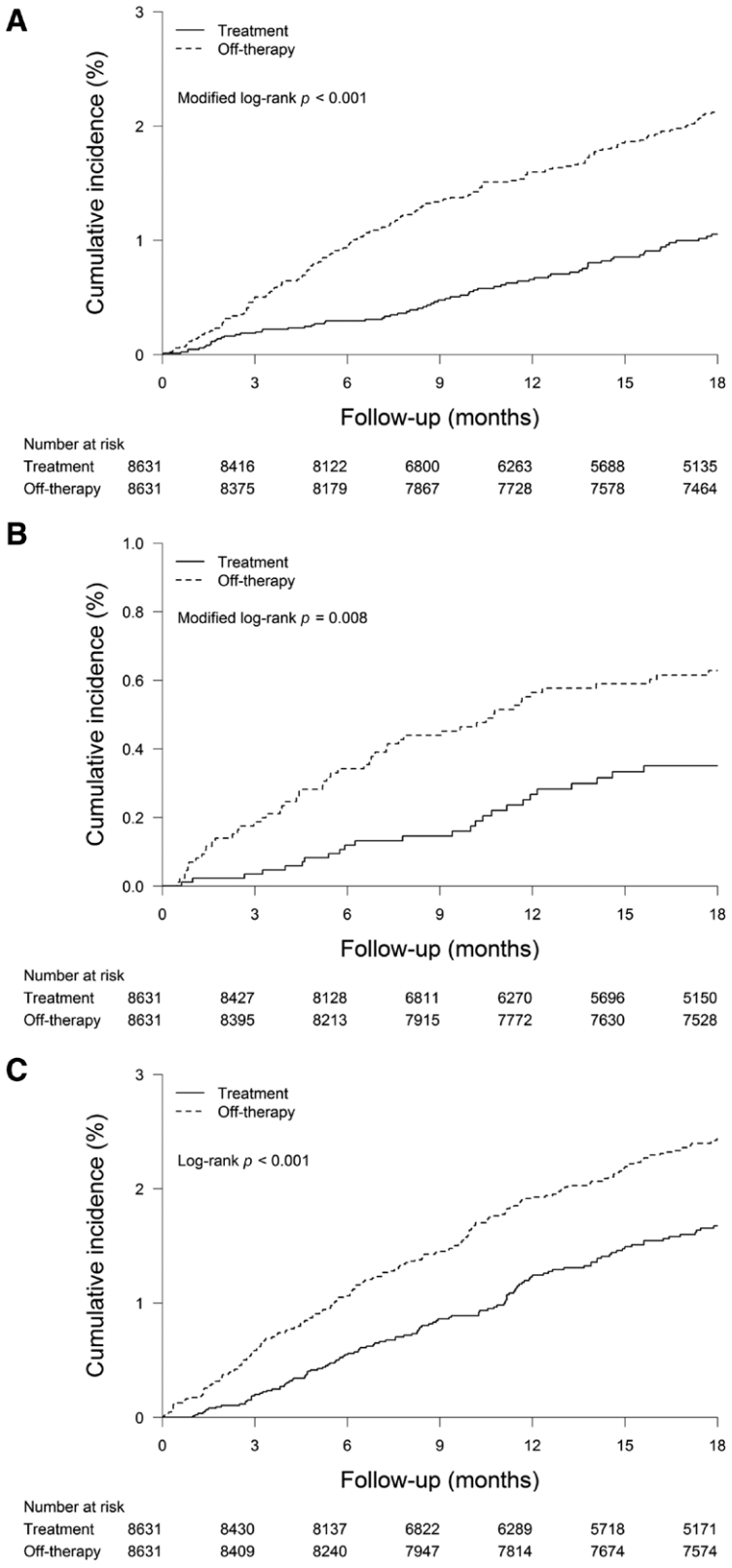


Fig. 1. Cumulative incidences of liver decompensation (A), hepatic failure (B), and death (C) after adjusting for competing mortality. Modified Kaplan-Meier method and Gray's method were used to calculate and compare cumulative incidences. Both the treatment cohort and off-therapy cohort were followed up from the index date, the date 1.5 years after first NA prescription. NAs = nucleos(t)ide analogues.

Table 2

Multivariable Cox proportional hazards model analysis for risk of liver decompensation after adjusting for competing mortality

	Hazards Ratio[a]	95% CI	*p*
Treatment vs off-therapy cohort	0.47	0.36–0.62	<0.001
Age, per each incremental year	1.06	1.05–1.07	<0.001
Male	1.48	1.10–2.00	0.010
Liver cirrhosis	4.51	3.31–6.14	<0.001
Renal failure	2.48	1.30–4.72	0.006
Diabetes	1.47	1.01–2.14	0.046
Peptic ulcer disease	1.23	0.86–1.75	0.260
Chronic obstructive pulmonary disease	1.18	0.63–2.20	0.610
Hypertension	1.00	0.68–1.47	1.000
Acute coronary syndrome	0.75	0.40–1.39	0.360
Hypercholesterolemia	0.45	0.06–3.28	0.430

[a] Adjusted for covariate factors, including age, gender, and comorbidities.

Table 3

Multivariable Cox proportional hazards model analysis for risk of hepatic failure after adjusting for competing mortality

	Hazards Ratio[a]	95% CI	*p*
Treatment vs off-therapy cohort	0.53	0.33–0.86	0.010
Age, per each incremental year	1.02	1.00–1.04	0.120
Male	1.37	0.78–2.40	0.270
Liver cirrhosis	2.03	0.90–4.58	0.089
Renal failure	0.96	0.11–8.04	0.970
Diabetes	0.85	0.29–2.46	0.760
Peptic ulcer disease	1.25	0.55–2.83	0.600
Chronic obstructive pulmonary disease	1.25	0.34–4.64	0.740
Hypertension	0.66	0.22–2.05	0.480
Acute coronary syndrome	1.69	0.46–6.17	0.430
Hypercholesterolemia	1.87	0.25–14.0	0.540

[a]Adjusted for covariate factors, including age, gender, and comorbidities.

Table 4

Multivariable Cox proportional hazards model analysis for overall mortality

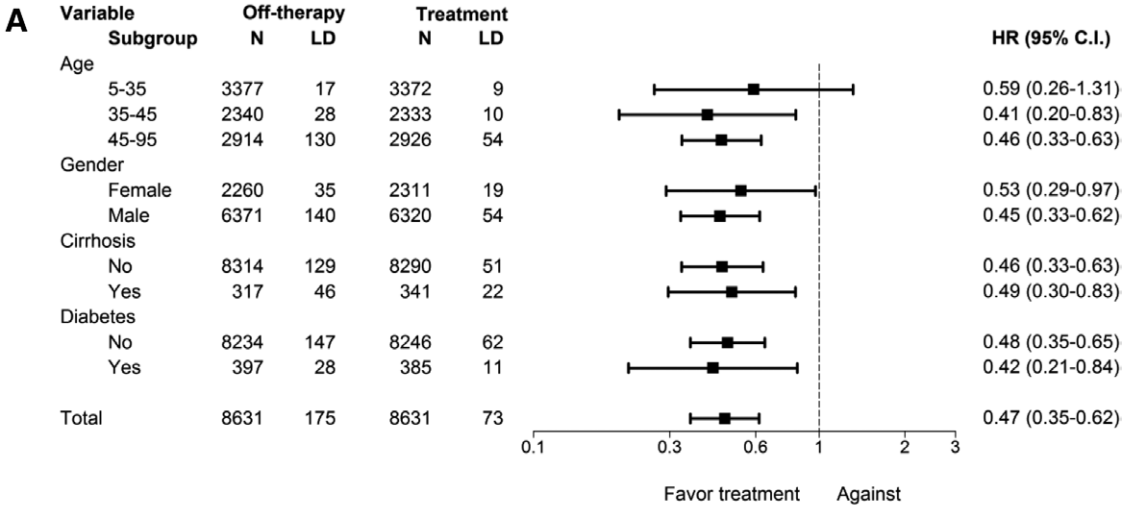
	Hazards Ratio[a]	95% CI	*p*
Treatment vs off-therapy cohort	0.67	0.53–0.84	0.001
Age, per each incremental year	1.07	1.06–1.08	<0.001
Male	1.15	0.90–1.48	0.270
Liver cirrhosis	2.53	1.88–3.41	<0.001
Renal failure	1.53	0.79–2.96	0.200
Diabetes	1.16	0.81–1.64	0.420
Peptic ulcer disease	1.15	0.83–1.59	0.400
Chronic obstructive pulmonary disease	1.48	0.92–2.40	0.110
Hypertension	1.12	0.81–1.56	0.500
Acute coronary syndrome	0.74	0.44–1.25	0.260
Hypercholesterolemia	0.58	0.13–2.56	0.470

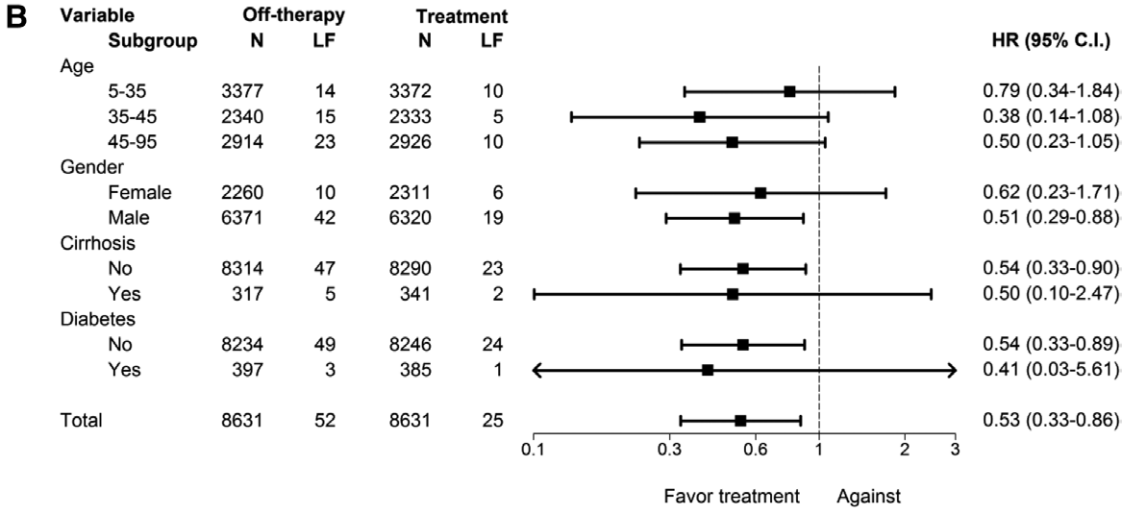
[a]Adjusted for covariate factors, including age, gender, and comorbidities.

of hepatitis B by Asian-Pacific Association for the Study of the Liver (APASL) recommends that extended consolidation therapy of NAs to 3 years after HBeAg seroconversion is preferable to achieve a more durable off-treatment response.[24] The APASL suggests that long-term NAs treatment, irrespective of HBeAg seroconversion status, appears to be necessary for HBeAg-positive CHB patients.

For patients with HBeAg-negative CHB, infinite and long-term treatment is recommended by most of the treatment guidelines because most of these patients will have a hepatitis relapse when NAs are discontinued.[17,19,20] In the APASL 2012 consensus statement, continuous NA treatment for HBeAg-negative CHB until serum HBV DNA becomes undetectable for three sessions that are 6 months apart is suggested, with economic cost as a major consideration.[30] According to this criterion, 1-year off-therapy leads to a 57.9% virological relapse, 45.3% clinical relapse, and 2.6% decompensation rate, respectively.[31] The cumulative incidences of hepatic decompensation and liver failure may increase incrementally after discontinuation of NAs and partially offset the initial beneficial effects of NAs therapy. Jeng et al.[20] further showed that CHB patients who received NA treatment for >3 years combined with a consolidation therapy (the duration from the date of first undetectable serum HBV DNA level to the end of treatment) of at least 2 years had an acceptable lower rate (30%) of clinical relapse 1 year after the discontinuation of therapy. Conversely, the 1-year relapse rate was 81% in their counterparts who had a shorter treatment or consolidation duration. In addition to the treatment duration, several host and viral factors have been investigated to predict the durability of the effect in patients after discontinuation of NAs, including age, baseline and on-treatment serum HBV DNA and HBsAg levels, serum HBV RNA levels, HBV genotypes and mutations, hepatitis B core-related antigen, and HBV-specific T cell responses.[19,26,32–34] However, none of these markers have been widely validated.[17] This might be because most, if not all, of the patients with CHB would have hepatitis relapse after discontinuation of NA. One recent multi-center study comprising Asian patients with CHB demonstrated an extremely high rate of virological relapse after cession of NA therapy (91.4% in 48 weeks).[35] From these findings, it is suggested that NAs must be continued indefinitely until HBsAg seroclearance because there are no reliable stopping rules.

However, some recent studies demonstrated that for patients with CHB, the discontinuation of NAs would induce HBV-specific T cell responses, which in turn lead to favorable clinical outcomes, such as sustained virological response and HBsAg seroclearance.[16,18,33] The most critical concern after cessation of NA therapy is hepatic decompensation. In a recent report of patients who recovered from hepatitis flares with decompensation, 29.9% had clinical relapse, 16.2% had hepatitis flares, and 8.2% had hepatic decompensation after cessation of therapy for 1 year.[36] Although all patients with decompensation were rescued by timely retreatment in that study, a mortality rate of 13.5% within 6 months of hepatic decompensation, despite NAs treatment, was demonstrated in another study.[37] In real-world practice, it is not uncommon to see serious liver-related complications in patients who are unable to maintain regular follow-up after stopping NA therapy.[38] In our present study, discontinuation of therapy in the general risk population resulted in an annual incidence of liver decompensation for the off-therapy cohort of 1.42%, which is significantly >0.70% for treatment cohort. Moreover, the annual overall mortalities in the treatment cohort and off-therapy cohort were 1.11% and 1.63%, respectively. In this population-based cohort study, we clearly indicated the benefits of continuous NAs treatment. In two previous reports in which there was strong potency with high genetic barriers, NA use for a period of >3 years resulted in improvement in necroinflammation and fibrosis and even a reversal of cirrhosis.[8,39] Subsequent cohort studies also disclosed that long-term NA therapy could reduce the risk of developing liver cirrhosis, hepatic decompensation, and HCC for patients with CHB.[9,14] Moreover, long-term use of NAs has an excellent safety profile, with no increase in the risk of cancer.[40–42] Taken together, continous NA therapy might be the better treatment strategy for CHB patients, especially in the setting of cirrhosis.





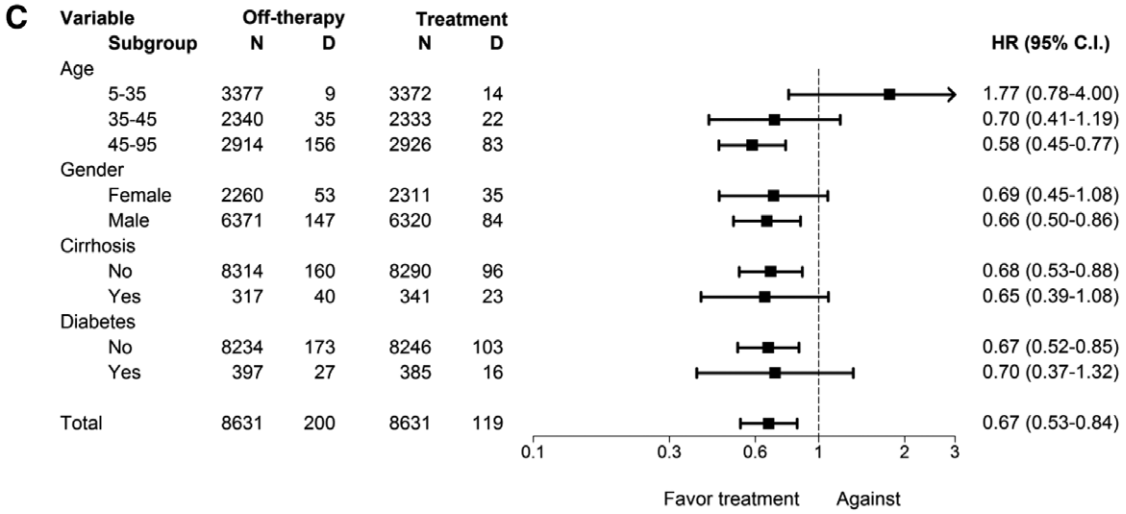


Fig. 2. Multivariate stratified analyses for the association between NA continuous therapy and liver decompensation (A), hepatic failure (B), and overall mortality (C). The protective effect of NA continuous therapy was found in nearly all subgroups. N = number; NA = nucleos(t)ide analogue; LD = liver decompensation; LF = liver failure; D = death.

There are some limitations in the present study. First, we used propensity score matching to select comparable cohorts to imitate a randomized control trial. Although all potential confounders have been used in the model to calculate the propensity score, some unmeasurable confounders may still exist because of the observational nature of our study design. Another limitation to the present study is that we did not have virological and liver function profiles, such as HBV viral load, and HBeAg status. Therefore, we could not investigate the treatment response, virological response, virological breakthrough, and the cause of death in our cohort. In addition, we could not identify the reason of discontinuation from NA therapy in our patients. We also cannot report virological and clinical relapse after NA discontinuation. To overcome this limitation, we focused on more important clinical outcomes, such as liver decompensation, hepatic failure, and overall mortality. The universal NIH policy for NA reimbursement was used to choose comparable cohorts while these patients received their initial 18-month NA therapy, including viral load and HBeAg status.[11,12]

In conclusion, we found that continuous NA treatment is associated with a reduced risks of liver decompensation, hepatic failure, and overall mortality in CHB patients. The number needed for one less disease progression or mortality within 18 months was <50. Furthermore, the protective effect of NA continuous therapy was found in nearly all subgroups.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1097/JCMA.0000000000000247.

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