Review

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Risk of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification with current antiviral therapy

George V. Papatheodoridis[1,*], Henry Lik-Yuen Chan[2], Bettina E. Hansen[3], Harry L.A. Janssen[3,4], Pietro Lampertico[5]

[1]*Academic Department of Gastroenterology, Athens University Medical School, Laiko General Hospital, Athens, Greece;* [2]*Department of Medicine and Therapeutics and Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong Special Administrative Region;* [3]*Department of Gastroenterology & Hepatology, Erasmus MC University Hospital, Rotterdam, The Netherlands;* [4]*Francis Family Liver Clinic, Toronto Western & General Hospital, Division of Gastroenterology, University of Toronto, Toronto, Canada;* [5]*1st Division of Gastroenterology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*

Summary

In the treatment of chronic hepatitis B (CHB), the ultimate goal is preventing hepatitis B virus (HBV)-associated liver disease, including hepatocellular carcinoma (HCC). Recently published studies show that in CHB patients treated with the currently recommended first-line nucleos(t)ide analogs (NAs) entecavir or tenofovir, annual HCC incidences range from 0.01% to 1.4% in non-cirrhotic patients, and from 0.9% to 5.4% in those with cirrhosis. In Asian studies including matched untreated controls, current NA therapy consistently resulted in a significantly lower HCC incidence in patients with cirrhosis, amounting to an overall HCC risk reduction of ~30%; in non-cirrhotic patients, HCC risk reduction was overall ~80%, but this was only observed in some studies. For patients of Caucasian origin, no appropriate comparative studies are available to date to evaluate the impact of NA treatment on HCC. Achievement of a virologic response under current NA therapy was associated with a lower HCC risk in Asian, but not Caucasian studies. Studies comparing entecavir or tenofovir with older NAs generally found no difference in HCC risk reduction between agents, except for one study which used no rescue therapy in patients developing lamivudine resistance. Overall, these data indicate that with the current, potent NAs, HCC risk can be reduced but not eliminated, probably due to risk factors that are not amenable to change by antiviral therapy, or events that may have taken place before treatment initiation. Validated pre- and on-therapy HCC risk calculators that inform the best practice for HCC surveillance and facilitate patient counseling would be of great practical value.

Introduction

Despite the dramatic improvement in the management of chronic hepatitis B (CHB), hepatocellular carcinoma (HCC) remains a major cause of morbidity and mortality, accounting for around 350,000 deaths worldwide every year [1,2]. Natural history studies in untreated patients have reported annual HCC incidences of 0.3–0.6% in non-cirrhotic patients, and 2.2–3.7% in compensated cirrhotic patients, with the highest rates observed in Asia [2].

The mechanism of hepatitis B virus (HBV)-related hepatocarcinogenesis is thought to involve several factors [3–5]. HBV DNA sequences integrate into the host genome, which may downregulate tumor suppressor genes. Recent studies have shown that integrated HBV is more frequent in HCCs than in adjacent liver tissue, with host integration sites located at cancer-related genes, including the telomerase reverse transcriptase (*TERT*) gene, and viral breakpoints detected near the *HBx* gene [6,7]. The viral protein HBx may modulate the activity of several cellular factors regulating cell proliferation, apoptosis, and DNA damage response. Fibrosis and mainly cirrhosis, resulting from CHB-associated persistent liver inflammation, trigger a complex cascade of oxidative stress, hypoxia, necrosis, regeneration, and angiogenesis, which may alter host gene expression.

Epidemiologic studies have confirmed sustained viral replication and liver injury as key risk factors for HBV-related HCC, with serum HBV DNA levels directly correlating with the future risk of HCC [8,9]. Specific variations in the HBV DNA sequence, such as HBV genotype C and basal core promoter (BCP) mutations have also been associated with a higher HCC risk [10–12]. In addition

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* Corresponding author. Address: Academic Department of Gastroenterology, Athens University Medical School, Laiko General Hospital, 17 Agiou Thoma Street, 115 27 Athens, Greece. Tel.: +30 210 7456315; fax: +30 210 7462601.
E-mail address: gepapath@med.uoa.gr (G.V. Papatheodoridis).

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; BCP, basal core promoter; NA, nucleos(t)ide analog; HR, hazard ratio; PS, propensity score; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; REVEAL, Risk Evaluation of Viral Load Elevation and Associated Liver Disease; CU-HCC, Chinese University – Hepatocellular Carcinoma score; GAG-HCC, Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis; ALT, alanine aminotransferase; ADV, adefovir; comb, combination therapy; comp, compensated; ETV, entecavir; LdT, telbivudine; LVD, lamivudine; NA, not assessed; TDF, tenofovir; tx, treatment; cirr, cirrhosis; decomp, decompensated; exp., experienced; NR, not reported; RR, risk reduction; VR, virologic response; A, Asian; C, Caucasian; yr, year.

to these viral factors, older age, male gender, heavy alcohol consumption, exposure to carcinogens such as aflatoxin B, a family history of HCC, and more recently, elevated levels of quantitative HBsAg (qHBsAg). Metabolic syndrome associated with obesity and diabetes mellitus have also been established as risk factors of HBV-related HCC [2,13–15]. Many of these factors are directly or indirectly related to viral replication, which becomes a logical target for HCC prevention.

Until recently, evidence of reduction of HCC incidence with antiviral treatment had been limited to the older nucleos(t)ide analogs (NAs) lamivudine and adefovir. The first important data to demonstrate the efficacy of anti-HBV therapy in HCC risk reduction are those from the randomized controlled trial by Liaw *et al.* which compared lamivudine *vs.* placebo in NA-naive patients with cirrhosis or advanced fibrosis and active liver disease. After an early trial termination with a mean treatment duration of approximately 3 years, lamivudine reduced the HCC risk compared with placebo by 51% (HCC incidence 3.9% *vs.* 7.4%), offering a benefit of marginal statistical significance (hazard ratio [HR] = 0.49; $p = 0.047$) [16]. Similar results were reported in other studies with older NAs. In a systematic review assessing mostly lamivudine (sometimes adefovir or the combination of both) *vs.* no treatment in NA-naive CHB patients, HCC incidence rates over a follow-up of 4 years were reduced in treated patients (2.8%) compared with untreated patients (6.4%; $p = 0.003$) [17]. A more recent meta-analysis also reported HCC rates of 3.4% in lamivudine-treated *vs.* 9.6% in untreated CHB patients over a follow-up of 4 years [18].

The NAs entecavir and tenofovir, currently recommended as first-line options for the treatment of CHB [19–21], maintain long-term viral suppression in over 95% of patients, improve liver histology, and often reverse histologic cirrhosis [22–24]. However, their effect on HCC risk remains unclarified. This review summarizes recent studies assessing HCC development with these current NAs, mainly entecavir due to data availability, and explores whether mathematical models to estimate the HCC risk may be applicable to the management of CHB patients at risk of HCC.

Key Points

- Hepatocellular carcinoma (HCC) may still develop in chronic hepatitis B (CHB) patients treated with oral antiviral agents
- In CHB patients treated with the currently recommended first-line antivirals entecavir or tenofovir, the observed HCC risk ranges from 0.01 to 1.4% in patients without cirrhosis, and from 0.9 to 5.4% in those with cirrhosis
- In Asian studies including matched untreated controls, treatment, and particularly treatment-induced virologic remission, with entecavir or tenofovir has been shown to reduce the risk of CHB-related HCC
- To date, there are no appropriate comparative studies evaluating the impact of these agents on HCC in CHB patients of Caucasian origin
- Accurate predictors or calculators of HCC risk under anti-HBV treatment may facilitate patient counseling and would be of great practical value

Impact of entecavir and tenofovir on HBV-related HCC

Recently, several studies have been published that assessed outcomes of HCC in patients treated with the NAs entecavir or tenofovir. In the following, we will review those reports that were published in English up to July 2014 (Supplementary Table 1). For published papers, PubMed was searched using the terms 'HCC', 'hepatocellular carcinoma', 'hepatitis B', 'HBV', 'antiviral therapy', 'entecavir', or 'tenofovir'; in addition, a manual search for AASLD and EASL 2012–2014 conference abstracts was performed using the same search terms. Studies were included in this review if they involved a minimum of 100 patients, used entecavir or tenofovir, and either had a control arm or, if single-arm, reported separate HCC rates for cirrhotic and non-cirrhotic patients. Potential reports selected in the literature search were evaluated by a second reviewer to determine whether they fulfilled the inclusion criteria. Most of the studies included in this review involved entecavir, which has been available for CHB treatment longer than tenofovir. Of these studies, none was a randomized trial, but most were observational studies reporting HCC outcomes in entecavir-treated patients using as control either untreated patients, or patients treated with one of the older NAs lamivudine or adefovir.

HCC incidence under entecavir or tenofovir vs. no treatment

Five studies, all from East Asia, compared HCC incidence rates in patients receiving current NAs (mostly entecavir) with those in historical untreated control groups (Table 1) [25–29]. However, such studies are limited by potential differences in baseline characteristics that may affect the HCC risk in the two arms. Three of these studies have utilized propensity score (PS) matching of the cohorts to reduce these confounding effects [26,28,29].

Of the three studies using PS-matched controls, only the study by Hosaka *et al.* from Japan included a cohort treated exclusively with entecavir [26], while the other two studies assessed patients treated with several NAs including entecavir [28,29]. In the study by Hosaka *et al.* 25–29% of patients had pre-existing cirrhosis at baseline [26]. The cumulative 5-year HCC incidence in the overall patient population was significantly lower with entecavir (3.7%) than with no treatment (13.7%; $p < 0.001$), with a >60% reduction in HCC risk (adjusted HR = 0.37; $p = 0.03$) [26]. When the analysis was stratified by the presence of cirrhosis, entecavir reduced the HCC risk more than 4-fold in cirrhotic patients (cumulative 5-year HCC incidence: 7.0% *vs.* 38.9%; $p < 0.001$), whereas the difference was much more modest and non-significant in non-cirrhotic patients (cumulative 5-year HCC incidence 2.5% *vs.* 3.6%; $p = 0.44$) [26]. Kumada *et al.* (Japan) used a treated cohort including patients receiving entecavir (61%) or lamivudine with or without adefovir (39%), and a PS-matched cohort of untreated patients. The overall 5-year HCC incidence was significantly lower with NA therapy than without (2.7% *vs.* 11.3%; $p < 0.01$), with a risk reduction of >70% (HR = 0.28; $p < 0.01$) [28]. A nationwide study from Taiwan (Wu *et al.*) assessed PS-matched cohorts of NA-treated patients (27% entecavir, 60% lamivudine, 1% telbivudine, 12% combination therapy) and patients receiving no NA therapy but hepatoprotective agents (e.g. silymarin, liver hydrolysate, or choline bitartrate). The 7-year HCC incidence was significantly lower in the NA-treated cohort (7.3%) than in the untreated cohort (22.7%) (adjusted HR = 0.37; $p < 0.001$). The beneficial effect of NA treatment was apparent in both patients with and

Table 1. HCC outcomes in treated *vs.* untreated patients.

Study	Treatment	N	Follow-up, yr, median (range)	HCC incidence, %*			HCC with *vs.* without NA treatment		
				3-yr	5-yr	7-yr	All pts	Cirrhosis	No cirrhosis
Hosaka [26] (Japan) NA-naive Historical, PS-matched control	ETV	Total: 316 No cirrhosis: 237 Cirrhosis: 79	3.3 (2.3–4.3)	1.2 0 4.3	3.7 2.5 7	n.r.	5-year incidence 3.7% *vs.* 13.7% p <0.001 HR = 0.37 p = 0.03	5-year incidence 7.0% *vs.* 38.9% p <0.001	5-year incidence 2.5% *vs.* 3.6% p = 0.44
	No tx	Total: 316 No cirrhosis: 231 Cirrhosis: 85	7.6 (3.4–13.7)	7.2 1.6 20.9	13.7 3.6 38.9	n.r.			
Wong [25] (Hong Kong) NA-naive and experienced Historical control	ETV	Total: 1446 No cirrhosis: 984 Cirrhosis: 482	3.0†	3.9 1.4 9.1	6.6 3.3 13.8	n.r.	5-year incidence 6.6% *vs.* 6.5%	5-year incidence 13.8% *vs.* 26.4% p = 0.036 HR = 0.55 p = 0.049	5-year incidence 3.3% *vs.* 3.0%
	No tx	Total: 424 No cirrhosis: 355 Cirrhosis: 69	9.5†	3.7 1.7 14.5	6.5 3.0 26.4	n.r.			
Su [27] (Taiwan) NA-naive Historical control	ETV	Cirrhosis: 666 (all comp)	2.7†	2.4	n.r.	n.r.	n.r.	2.7-year incidence 2.4% *vs.* 5.2% p = 0.009 HR = 0.41	n.r.
	No tx	Cirrhosis: 621 (all comp)	9.1†	5.2	n.r.	n.r.			
Kumada [28] (Japan) NA-naive Historical, PS-matched control	NAs (61% ETV, 15% LVD, 24% LVD+ADV)	Total: 117 No cirrhosis: 69 Cirrhosis: 48	12.3 (3.1–19.4)	n.r.	2.7	3.3	10-year incidence 3.3% *vs.* 40.0% p = 0.0094 HR = 0.28 p = 0.002	n.r.	n.r.
	No tx	Total: 117 No cirrhosis: 73 Cirrhosis: 44	11.6 (3.1–18.3)	n.r.	11.3	26.0			
Wu [29] (Taiwan) (Previous treatment exposure not specified)	NAs (27% ETV, 60% LVD, 1% LdT, 12% comb); hepato-protective agents	Total: 21,595 No cirrhosis: 18,748 Cirrhosis: 2847	3.34 (1.40–5.50)	n.r.	n.r.	7.3	7-year incidence 7.3% *vs.* 22.7% HR = 0.37 p <0.001	HR = 0.72	HR = 0.27
Historical, PS-matched control	Hepato-protective agents	Total: 21,595 No cirrhosis: 18,579 Cirrhosis: 3016	6.51 (3.54–7.00)	n.r.	n.r.	22.7			

Areas shaded in light-grey indicate consistent data. *Data shown are for total study population, and if reported, for subgroups of patients with no cirrhosis and cirrhosis. †Mean. ADV, adefovir; comb, combination therapy; comp, compensated cirrhosis; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; LdT, telbivudine; LVD, lamivudine; NAs, nucleos(t)ide analogs; n.r., not reported; PS, propensity score; TDF, tenofovir; tx, treatment.

without cirrhosis (non-cirrhosis: HR = 0.27; cirrhosis: HR = 0.72) [29].

The two studies comparing entecavir-treated patients and untreated historical controls without detailed matching reported significant reduction in the HCC rates in cirrhotic patients. An observational study from Hong Kong by Wong *et al.* assessed the impact of entecavir *vs.* no treatment in a mixed population of NA-naive and NA-experienced (30%) patients. Pre-existing cirrhosis was detected in 33% of entecavir-treated and in 16% of untreated patients. Although there was no significant difference in HCC incidence between entecavir-treated and untreated patients in the overall comparison, when the analysis was stratified by cirrhosis, entecavir significantly reduced the HCC incidence in cirrhotic (5-year incidence 13.8% *vs.* 26.4%; HR = 0.55; p = 0.049), but not in non-cirrhotic patients (5-year incidence 3% in both groups) [25]. An observational multi-center study in compensated cirrhotics from Taiwan compared patients receiving first-line entecavir with an untreated historical control group. The HCC incidence in the first 2.7 years was 2.4% in the entecavir group and 5.2% in the untreated group (p = 0.009), corresponding to an HCC risk reduction by ~60% (HR = 0.41; 95% CI 0.20–0.84) [27].

Another approach to assess the impact of NA therapy *vs.* no treatment on HCC development is to compare the HCC incidence observed in treated patients with that predicted by a risk calculator. This method was used by Kim *et al.* [30], who compared the HCC incidence reported in the global tenofovir Phase III studies in NA-naive patients with the HCC incidence estimated by the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) risk calculator based on individual patients' characteristics [31]. Among 641 patients included in these studies, there were 13 cases of HCC over 6 years of tenofovir therapy. The 10th HCC case occurred at 3.3 years, at which time the REACH-B model predicted 11.2 cases. Beyond that time point, there was a progressive divergence between the predicted and observed number of HCC cases (standardized incidence ratio = 0.55 [95% confidence interval 0.32–0.94] after a median follow-up of 5.5 years) [30]. One limitation of this study is that the REACH-B model was developed in Asian non-cirrhotic patients [31], whereas the tenofovir trials included mostly white patients (59% Whites, 30% Asians) and 28% cirrhotic patients [24,32].

HCC incidence in relation to on-therapy virologic remission

An alternative way of assessing the impact of antiviral therapy on HCC risk is to correlate the degree of viral suppression with subsequent development of HCC. This approach has been used by seven studies; four from East Asia and three from Europe (Table 2) [25,33–38]. Of these, six used exclusively entecavir, whereas one study also involved other NAs; in the latter study, all patients were NA-naive, whereas in the other six, patients could be NA-naive or NA-experienced.

The study in NA-naive patients came from Korea, and included treatments with various NAs (73% entecavir, 5% lamivudine, 3.5% clevudine, 18.7% with sequential or combination therapy), which achieved a virologic response (VR) in 82.5% of patients. In addition, a control group of inactive HBV carriers (HBeAg-negative) was included. Among treated patients, HCC incidence was significantly higher among those who did not achieve a VR than in those who did ($p = 0.028$), with a significant treatment effect observed in the subgroup of cirrhotic patients ($p = 0.004$), but not in non-cirrhotics. However, treated patients with a VR still had a significantly higher HCC risk compared with inactive carriers (overall annual HCC incidences 2.3% *vs.* 0.3%; $p < 0.001$) [35].

Similar findings were observed in the Asian studies including both NA-naive and NA-experienced patients. In a Taiwanese cohort study of entecavir-treated patients (Yang *et al.*; 33.6% NA-experienced; 40% cirrhotic), the cumulative incidences of HCC were lower with achievement of a VR in both non-cirrhotic (HR = 0.08; $p = 0.001$) and cirrhotic patients (HR = 0.21; $p = 0.001$) [33]. In another study from Korea by Kim *et al.* including entecavir-treated cirrhotic CHB patients, VR was associated with a significantly lower probability of developing HCC (HR = 0.06; $p < 0.001$) [34]. The Hong Kong study by Wong *et al.* described earlier reported that in the entecavir group, virologic remission had no impact on the HCC rate in the overall patient population (8.7% *vs.* 10.7%, $p = 0.33$), but was associated with a significantly reduced probability of HCC in the subgroup of cirrhotic patients ($p = 0.02$) [25].

In Caucasian CHB patients, the benefit of virologic remission was controversial. A large European study (VIRGIL) evaluated entecavir-treated patients (23% NA-experienced; 22% cirrhotic; 42% Caucasian, 29% Asian, 29% other/unknown) [37]. After a follow-up of 1.7 years, patients achieving a VR to entecavir had a 71% lower probability of a clinical event (HCC, hepatic decompensation, or death) than those who did not (HR = 0.29; $p = 0.05$), with a significantly reduced risk among cirrhotic patients (HR = 0.22; $p = 0.04$), but not in those without cirrhosis [36]. However, after prolonged follow-up to year 3, an association between virologic suppression and HCC (HR = 0.87; $p = 0.87$) or clinical event (HR = 0.70; $p = 0.46$) in the overall study population was no longer observed [37]. Finally, in a study from Greece including NA-naive or NA-experienced patients treated with entecavir, virologic remission was achieved in 97% of cases and was reported not to affect the HCC incidence, but the number of patients without remission was rather small [38].

HCC incidence under entecavir or tenofovir vs. older NAs

Seven studies addressed whether entecavir or tenofovir are more effective in reducing HCC risk than older NAs (Table 3). Four of these studies were from East Asia [26,39–41], two from Turkey [42,43], and one from Greece [38]. The study by Hosaka *et al.* in NA-naive patients also included a comparison between entecavir-treated patients and historical controls receiving lamivudine without any rescue therapy upon resistance (182 PS-matched patients in each group); in non-cirrhotic patients, HCC rates were comparable between entecavir and lamivudine; however, in cirrhotic patients, the HCC incidence was significantly lower with entecavir than with lamivudine ($p = 0.04$) [26]. The study by Kobashi *et al.* from Japan included NA-naive patients treated with entecavir or lamivudine (47% with rescue therapy; baseline cirrhosis 22% and 27%, respectively). After a treatment duration of 4 years, there was no significant difference in the overall HCC incidence between entecavir and lamivudine. However, lamivudine resistance, which developed in 60/127 (47%) lamivudine-treated patients, was associated with a significantly increased risk of HCC (20.3% *vs.* 3.2% at year 5; $p = 0.04$; [39]). A Korean analysis of PS-matched pairs of NA-naive patients treated with entecavir or lamivudine (39% with rescue therapy) found that in the overall study population, and in patients with cirrhosis, the risk of death or transplantation was 50–60% lower with entecavir than with lamivudine ($p < 0.001$) after 3 years of follow-up; however, HCC risk over the same time period was comparable between the two treatments. In patients without cirrhosis, there was no difference between treatments for both outcomes [40]. Another Korean study in patients treated with either entecavir or lamivudine (proportion of patients with rescue therapy not reported) also found no significant difference in HCC incidence between entecavir (6.5%) and lamivudine (7.3%) after 2.5 years of therapy ($p = 0.131$), despite higher rates of undetectable HBV DNA and lower resistance with entecavir [41].

An ongoing nationwide study in Greece (HEPNET) assessed HCC incidence in a mixed (24% NA-experienced; 25% cirrhotic) cohort of HBeAg-negative patients treated with entecavir, compared with that in an historical cohort of lamivudine-treated patients (49% with rescue therapy). In the overall population, HCC incidence was lower with entecavir than with lamivudine (2.8% *vs.* 5.6% at year 5; $p = 0.024$), but the difference could not reach statistical significance when the treatment effect was evaluated separately in non-cirrhotic patients (0.5% *vs.* 3.2% at year 5; $p = 0.091$) and cirrhotic patients (9.3% *vs.* 11.5% at year 5; $p = 0.277$). In a multiple regression analysis, HCC risk was not associated with antiviral agent type [38]. A Turkish study (Köklü *et al.*) assessed the impact of entecavir, tenofovir, and lamivudine (32% with rescue therapy) in NA-naive and -experienced (14%) patients with cirrhosis. Over 3 years of follow-up, the HCC incidence was comparable between the three agents [42]. In another Turkish study comparing NAs with a high (entecavir or tenofovir) or low (lamivudine or adefovir; proportion of patients with rescue therapy not reported) genetic barrier, HCC development was significantly associated with low genetic barrier drug regimens ($p = 0.02$) and resistance-associated virologic breakthrough ($p = 0.04$) [43].

Summary of annual HCC rates under entecavir or tenofovir

The annual HCC rates under entecavir or tenofovir reported in these studies, and in single-arm studies assessing HCC outcomes during treatment with these NAs [44–46], are shown separately for non-cirrhotic and cirrhotic patients in Fig. 1A and B. In non-cirrhotic patients treated with entecavir or tenofovir, annual HCC incidences ranged from 0.0% to 1.4% in Asian patients, and from 0.1% to 1.0% in predominantly Caucasian populations. In cir-

Table 2. HCC outcomes in treated patients with *vs.* without virologic response.

Study	Treatment	N	Follow-up, yr, median (range)	VR*	HCC incidence, %†			HCC with *vs.* without NA treatment		
					3-yr	5-yr	7-yr	All pts	Cirrhosis	No cirrhosis
Wong [25] (Hong Kong) Tx-naive + -experienced	ETV	Total: 1446 No cirrhosis: 984 Cirrhosis: 482	3.0‡	+ VR: 77%	8.7	n.r.	n.r.	3-year incidence 8.7% *vs.* 10.7% *p* = 0.33	3-year incidence *p* = 0.02	n.r.
				– VR: n.r.	10.7	n.r.	n.r.			
Yang [33] (Taiwan) Tx-naive + -experienced	ETV	Total: 323 No cirrhosis: 202 Comp cirrhosis: 106 Decomp cirr: 15	3.0 (1.0–6.0)	+ VR: 83-98%	n.r.	n.r.	n.r.	n.r.	HR = 0.08 *p* = 0.001	HR = 0.21 *p* = 0.001
				– VR: n.r.	n.r.	n.r.	n.r.			
Kim [34] (Korea) Tx-naive + -experienced	ETV	Cirrhosis: 324 Comp cirrhosis: 220 Decomp cirr: 104	3.0‡	+ VR: n.r.	n.r.	n.r.	n.r.	n.r.	RR = 0.056 *p* <0.001	n.r.
				– VR: n.r.	n.r.	n.r.	n.r.			
Cho [35] (Korea) Tx-naive	NAs (73% ETV, 5% LVD, 22% other)	Total: 1378 No cirrhosis: 933 Cirrhosis: 445	3.3‡	+ VR: 82%	5.9 4.7 8.1	11.4 7.2 17.4	n.r.	5-year incidence 11.4% *vs.* 18.8% *p* = 0.028	5-year incidence 17.4% *vs.* 38.7% *p* = 0.004	5-year incidence 7.2% *vs.* 11.1% *p* = 0.212
				– VR: 18%	8.6 6.4 14.3	18.8 11.1 38.7	n.r.			
Zoutendijk [36] (Europe) Tx-naive + -experienced	ETV	Total: 372 No cirrhosis: 274 Comp cirrhosis: 98	1.7 (0.9–2.7)	+ VR: 93%	n.r.	n.r.	n.r.	HR = 0.29 *p* = 0.05	HR = 0.22 *p* = 0.04	HR = 0.24 *p* = 0.27
				– VR: n.r.	n.r.	n.r.	n.r.			
Arends [37] (Europe) Tx-naive + -experienced	ETV	Total: 744 No cirrhosis: 580 Cirrhosis: 164	3.2 (1.6–4.1)	+ VR: 99%	n.r.	n.r.	n.r.	HR = 0.87 *p* = 0.87	n.r.	n.r.
				– VR: n.r.	n.r.	n.r.	n.r.			
Papatheodoridis [38] (Greece) Tx-naive + -experienced	ETV	Total: 321 No cirrhosis: 212 Comp cirrhosis: 55 Decomp cirr: 14 Unclassified: 40	3.3 (2.1–4.3)	+ VR: 97%	n.r.	n.r.	n.r.	5-year incidence n.s.	n.r.	n.r.
				– VR: n.r.	n.r.	n.r.	n.r.			

Areas shaded in light-grey indicate consistent data. *Data shown are for total study population. †Data shown are for total study population, and if reported, for subgroups of patients with no cirrhosis and cirrhosis. †Mean. ADV, adefovir; cirr, cirrhosis; comb, combination therapy; comp, compensated cirrhosis; decomp: decompensated cirrhosis; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; LdT, telbivudine; LVD, lamivudine; NAs, nucleos(t)ide analogs; NR, not reported; PS, propensity score; RR, risk reduction; TDF, tenofovir; tx, treatment; VR, virologic response.

Table 3. HCC outcomes with current NAs *vs.* older NAs.

Study	Treatment	N	Follow-up, yr; median (range)	HCC incidence, %*			HCC with current *vs.* older NAs		
				3-yr	5-yr	7-yr	All pts	Cirrhosis	No cirrhosis
Hosaka [26] (Japan) Tx-naive Historical, PS-matched control	ETV (rescue therapy: none)	Total: 316 No cirrhosis: 237 Cirrhosis: 79	3.3 (2.3–4.3)	1.2 0 4.3	3.7 2.5 7.0	n.r.	5-year incidence 7.0% *vs.* 22.2% $p = 0.043$	5-year incidence 7.0% *vs.* 22.2% $p = 0.043$	5-year incidence 2.5% *vs.* 4.9% $p = 0.126$
	LVD (rescue therapy: none)	Total: 182 No cirrhosis: 97 Cirrhosis: 85	6.8 (5.0–9.9)	n.r. 3.2 12.2	n.r. 4.9 22.2	n.r.			
Kobashi [39] (Japan) Tx-naïve	ETV (rescue therapy: <1%)	Total: 129 No cirrhosis: 101 Cirrhosis: 28	2.9 (0.4–7.5)	7.0	11.8	n.r.	5-year incidence 11.8% *vs.* 11.7% $p = 0.680$	n.r.	n.r.
	LVD (rescue therapy: 47%)	Total: 127 No cirrhosis: 93 Cirrhosis: 34	6.0 (0.5–10.0)	6.4	11.7	n.r.			
Lim [40] (Korea) PS-matched Tx-naive + -experienced	ETV (rescue therapy: 1.8%)	Total: 1792 No cirrhosis: 878 Cirrhosis: 860	3.1 (2.2–4.3)	n.r.	n.r.	n.r.	Annual incidence 2.4% *vs.* 2.5% HR = 1.01 $p = 0.95$	Annual incidence 4.1% *vs.* 4.35% HR = 1.0 $p = 0.999$	Annual incidence 0.7% *vs.* 0.8% HR = 1.26 $p = 0.46$
	LVD (rescue therapy: 39.3%)	Total: 1792 No cirrhosis: 878 Cirrhosis: 860	8.7 (6.5–11.5)	n.r.	n.r.	n.r.			
Lee [41] (Korea) Previous tx not specified	ETV (rescue therapy: n.r.)	Total: 293	2.5	6.5% (yr 2.5)	n.r.	n.r.	2.5-year incidence 6.5% *vs.* 7.3% $p = 0.131$	n.r.	n.r.
	LVD (rescue therapy: n.r.)	Total: 165	2.4	7.3% (yr 2.4)	n.r.	n.r.			
Papatheodoridis [38] (Greece) Tx-naive + -experienced Historical control	ETV (rescue therapy: <1%)	Total: 321 No cirrhosis: 212 Comp cirrhosis: 55 Decomp cirr: 14 Unclassified: 40	3.3 (2.2–4.3)	1.2 0.5 } 3.3 -	2.8 0.5 } 9.3 -	n.r.	5-year incidence 2.8% *vs.* 5.6% $p = 0.024$	5-year incidence 9.3% *vs.* 11.5% $p = 0.277$	5-year incidence 0.5% *vs.* 3.2% $p = 0.091$
	LVD (rescue therapy: 49%)	Total: 818 No cirrhosis: 517 Comp cirrhosis: 160 Decomp cirr: 56 Unclassified: 85	4.7 (2.6–6.4)	3.8 1.7 } 8.5 -	5.6 3.2 } 11.5 -	n.r.	HR = 1.9 $p = 0.214$		
Goturk [43] (Turkey) Previous tx exposure not specified	ETV or TDF (rescue therapy: NA)	Total: 661 No cirrhosis: 436 Cirrhosis: 225	4 (1–7.8)	n.r.	n.r.	n.r.	Low barrier to resistance agent $p = 0.02$‡ Resistance/ virologic breakthrough $p = 0.04$‡	n.r.	n.r.
	LVD or ADV (rescue therapy: NA)			n.r.	n.r.	n.r.			
Köklü [42] (Turkey) Tx-naive + -experienced	ETV (rescue therapy: 2.6%)	Total: 77 No cirrhosis: 0 Comp cirrhosis: 41 Decomp cirr: 36	2.0†	4/77** (yr 2)	n.r.	n.r.	n.r.	n.r.	n.r.
	TDF (rescue therapy: 2.7%)	Total: 72 No cirrhosis: 0 Comp cirrhosis: 46 Decomp cirr: 26	1.8†	2/72** (yr 1.8)	n.r.	n.r.			
	LVD (rescue therapy: 32%)	Total: 74 No cirrhosis: 0 Comp cirrhosis: 34 Decomp cirr: 40	3.0†	6/74** (yr 3)	n.r.	n.r.			

Areas shaded in light-grey indicate consistent data. *Data shown are for total study population, and if reported, for subgroups of patients with no cirrhosis and cirrhosis. †Mean. ‡Multivariate regression analysis. **n/N.

ADV, adefovir; comb, combination therapy; comp, compensated cirrhosis; decomp: decompensated cirrhosis; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; LdT, telbivudine; LVD, lamivudine; NA, not assessed; NAs, nucleos(t)ide analogs; PS, propensity score; RR, risk reduction; TDF, tenofovir; tx, treatment.

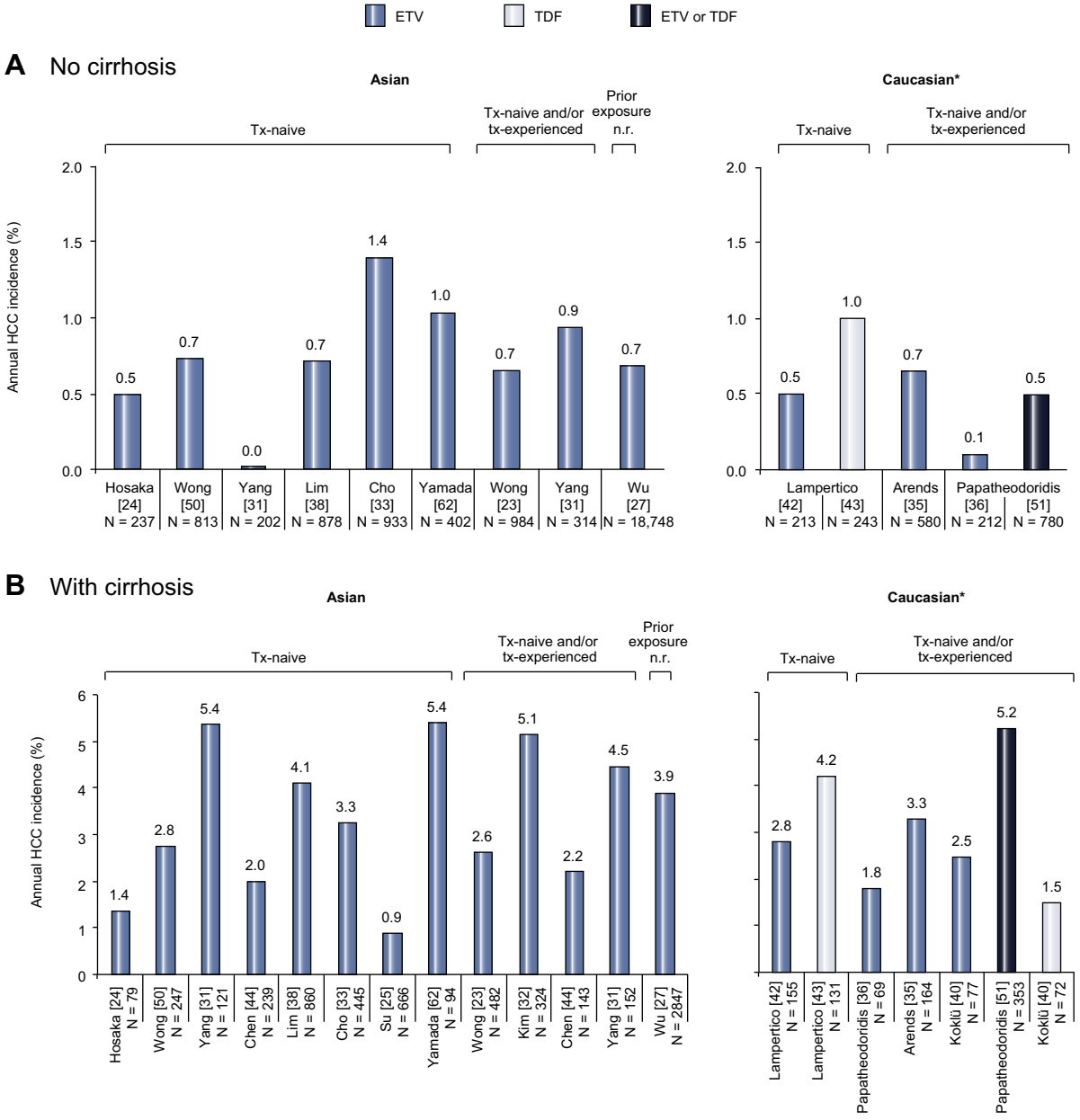

Fig. 1. Annual HCC incidence rates with entecavir or tenofovir in CHB without cirrhosis (A) and with cirrhosis (B). Annual HCC incidences were calculated from studies with different follow-up duration by assuming constant incidence rates over time. In panel B, the following studies reported rates for compensated cirrhotic patients only (decompensated excluded): Wong [25,53]; Yang, naive/experienced cohort [33]; Lampertico, ETV cohort [44]; Papatheodoridis, ETV/TDF cohort [54]. The following studies reported pooled rates for patients with compensated and decompensated cirrhosis, with the ratio of decompensated and compensated given in brackets: Yang, NA-naive cohort (15/106) [33]; Kim (104/220) [34]; Papatheodoridis, ETV cohort (14/55) [38]; Köklü, ETV cohort (36/41), TDF cohort (26/46) [42]. In the following studies the number of any decompensated patients that may have been included in the cirrhotic cohort is not reported: Hosaka [26]; Chen [46]; Lim [40]; Cho [35]; Su [27]; Wu [29]. *Proportions of Caucasian patients included in the study populations were: Lampertico, ETV cohort: >98% [Lampertico personal communication]; Lampertico, TDF cohort: 100% [Lampertico personal communication]; Arends: 42.5% [37]; Papatheodoridis ETV cohort >98% [Papatheodoridis personal communication], ETV/TDF cohort: 99.2% [54]; Köklü: not reported. (CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; n.r., not reported; TDF, tenofovir; tx, treatment).

rhotic patients treated with entecavir or tenofovir, HCC rates were around 4 to 5 times higher than in those without cirrhosis, ranging from 0.9% to 5.4% in Asians and from 1.5% to 5.2% in Caucasians. HCC rates in NA-naive patients were comparable to those in mixed populations of NA-naive and -experienced patients. This observation is in line with a Taiwanese study (Chen *et al.*) which assessed the HCC outcomes under entecavir in cirrhotic patients based on previous treatment exposure; HCC incidence was comparable between NA-naive and NA-experienced patients (15.8% *vs.* 11.1%; $p = 0.98$) [46].

Using those studies that assessed outcomes with and without NA treatment [25–27,29], all of which were Asian and with entecavir, we also compared the mean annual HCC incidences weighted according to the sample size of each study. In patients

with cirrhosis, the weighted mean annual HCC incidence was 3.2% with entecavir compared with 4.5% without treatment ($p = 0.004$); in patients without cirrhosis, the weighted mean annual HCC incidences with and without treatment were 0.68% and 2.90% ($p < 0.0001$), respectively. When considering only studies with a PS-matched control [26,29], the weighted mean annual HCC incidences were 3.83% with entecavir compared with 5.0% without treatment ($p = 0.028$) in patients with cirrhosis, and 0.68% *vs.* 2.94% ($p < 0.0001$) in those without cirrhosis.

Risk calculators for HBV-related HCC

Several scoring systems, most of which were derived from data on untreated Asian patients, have been developed to predict the risk of HBV-related HCC based on some of the known HCC risk factors (Table 4, [31,47–49]). The REACH-B score was based on data from the Taiwanese Risk Evaluation of Viral Load Elevation and Associated Liver Disease (REVEAL) cohort, and was subsequently validated in other independent Asian patient groups [31]. A revised version of REACH-B exists that also integrates serum qHBsAg levels [50]. Two other Asian scoring systems, Chinese University – Hepatocellular Carcinoma score (CU-HCC) (including 15% treated patients) and Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis (GAG-HCC), have been developed using data from two independent Hong Kong cohorts [47,48]. The latter two models highlight that cirrhosis is an important risk factor for HCC in Asians; although without a biopsy, detection of cirrhosis in routine practice is neither sensitive nor standardized [51]. Non-invasive measurements of liver fibrosis such as transient elastography may enhance the accuracy of these models; however, further studies are needed [52].

An important question is whether HCC risk predictors are also applicable in patients receiving antiviral therapy, as this generally results in HBV DNA suppression and sometimes also regression

Table 4. Comparisons of published risk scoring systems for HCC.

	CU-HCC (Wong *et al.*) [47]		GAG-HCC (Yuen *et al.*) [48]		REACH-B (Yang *et al.*) [31]		PAGE-B (Papatheodoridis *et al.*) [49]	
Number of patients	1005		820		3584		1619	
Place of development	Hong Kong		Hong Kong		Taiwan		Europe	
Ethnicity	Asian		Asian		Asian		Caucasian	
Age (years)	48.0		40.6		45.7		53	
HBeAg-negative (%)	Not reported		56.6		84.8		84	
Cirrhosis (%)	38.1		15.1		0		30	
Follow-up (years)	9.94		5.62		12.0		3.3	
Antiviral therapy (%)	15.1		0		0		100	
HCC (n, %)	105, 10.4		40, 4.9		131, 3.7		56, 3.5	
Scoring system	Variable	Points	Variable	Points	Variable	Points	Variable	Points
	Age >50 years	3	Age Per year	1 (1*)	Age Per 5 years over 30	1	Age <30 30–39 40–49 50–59 60–69 ≥70	 –4 –2 0 2 4 6
	Albumin <3.5 g/dl	20	Male	16 (14*)	Male	2	Male	5
	Bilirubin >1.1 mg/dl	1.5	*BCP* mutation	19	ALT, U/L 15–44 ≥45	 1 2	Platelets, mm^3 ≥200x10^3 100–<200x10^3 <100x10^3	 0 6 11
	Cirrhosis	15	Cirrhosis	30 (33*)	HBeAg-positive	2		
	HBV DNA 4–6 log >6 log	 1 4	HBV DNA Per log	3 (3*)	HBV DNA <4 log 4–<5 log 5–<6 log ≥6 log	 0 3 5 4†		
Risk scores	Low (<5), intermediate (5–20), and high (>20)		Low (<101) and high (≥101)		A 17-point risk scale		A 27-point risk scale (–4 to 22); low (<6), intermediate (6–10), and high (>10)	

*Simplified GAG-HCC score excluding core promoter mutations. †The risk score attributed to HBV DNA $\geqslant 10^6$ copies/ml was less than that for HBV DNA of 10^5–<10^6 copies/ml because most patients with HBV DNA $\geqslant 10^6$ copies/mL were also HBeAg-positive, thus sharing the associated higher score for this category. ALT, alanine aminotransferase; BCP, basal core promoter; CU-HCC, Chinese University – Hepatocellular Carcinoma score; GAG-HCC, Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis; HCC, hepatocellular carcinoma; REACH-B, Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B. HBV DNA presented as $\log_{10}$ copies/ml.

of cirrhosis [19–21]. The accuracy of REACH-B, CU-HCC, and GAG-HCC has been confirmed in entecavir-treated patients in one cohort from Hong Kong, and seems to increase from year 2 of therapy onwards compared with baseline [53]. However, these models were reported to offer poor accuracy for the prediction of HCC in European Caucasian patients receiving antiviral therapy [37,54]. In mostly Caucasian European patients under entecavir or tenofovir therapy, a new score named PAGE-B has recently been developed; in this score, which included age, gender, and platelet counts probably reflecting the severity of liver disease, the addition of cirrhosis did not substantially improve the discrimination [49].

The variables included in all these models can be conceptually divided into three categories: (i) variables that are readily modifiable by antiviral therapy, namely HBV DNA and alanine aminotransferase (ALT); (ii) variables that can potentially be altered with long-term antiviral therapy, namely albumin, bilirubin, platelets, HBeAg status, and, ultimately, cirrhosis; and (iii) variables that are not affected, namely age and gender. Examination of the weights associated with these variables may be instructive in estimating the impact on HCC risk that could potentially be attributed to antiviral therapy by the different risk scores. The CU-HCC model, in which four out of the five variables are modifiable by NAs, may suggest that most of the HCC risk may be eliminated with effective long-term antiviral therapy. In the GAG-HCC model, the relative impact on HCC risk of reversible components is much smaller. With the REACH-B score, out of the possible maximum score of 17, up to nine are potentially reversible. In PAGE-B, only one (platelets) of the three variables may be altered with antiviral therapy. Serum HBV DNA is included in three of the four models, and is also an important component of guideline recommendations to determine treatment candidacy [19–21]. In general, recent studies investigating predictors of HCC under NA therapy usually identified older age ($\geqslant$50–60 years), cirrhosis or advanced liver disease, male gender, family history of HCC, and previous lamivudine therapy as risk factors for HCC during NA therapy [37,38,55,56]. Importantly, baseline HBV DNA level was not associated with HCC risk [35,56], which is in contrast to studies assessing HCC risk in untreated patients [8,9], and highlights the importance of different HCC risk models for different patient populations.

Discussion

The data summarized in this review show that treatment with the current NAs entecavir and tenofovir can reduce the risk of HCC, which is consistent with prior data from the lamivudine era. The treatment effect was significant in patients with cirrhosis, whereas a significant HCC risk reduction in non-cirrhotic patients was noticeable only in some reports. Using only studies reporting comparative data with *vs.* without NA treatment, all of which were from Asia, treatment with a current NA resulted in a significant reduction of HCC risk by ~30% in cirrhotic patients, and by ~80% in non-cirrhotic patients. Although the data are limited, no substantial difference seemed evident between treatment-naive and -experienced patients.

The putative mechanisms of how antiviral therapy reduces HCC risk may include downregulation of hepatic inflammation and related nuclear signaling pathways that lead to neoplastic transformation at the cellular level, as well as reversal of fibrosis and reduction of regenerative stimuli at the tissue level. Antiviral therapy may also reduce expression of HBx protein to levels insufficient to promote HCC development, or act at a genomic level by preventing HBV DNA integration into host chromosomes or affecting its malignant potential [3–5].

The fact that antiviral therapy reduces HCC risk in cirrhotic patients is remarkable considering that cirrhosis is regarded as a pre-malignant condition [57]. Both entecavir and tenofovir have been shown to achieve reversal of cirrhosis over treatment periods of around 5 years [23,24]. However, the effect of antiviral therapy on HCC incidence in some of the studies appears to become evident before a significant amount of fibrosis regression is expected, which may suggest that some elements in the carcinogenesis process may be driven independently of histologic liver damage [58], as also evidenced by cases of HCC development in the absence of prior cirrhosis [59].

Regarding the HCC risk in patients without cirrhosis, findings were inconsistent between studies, with a significant treatment-induced risk reduction reported in some [29,33], but not in other reports [25,26,35]. The lack of treatment effect in non-cirrhotic patients may be due to insufficient statistical power relating to the lower HCC incidence in these patients, and a relatively short follow-up. On the other hand, one of the studies which observed a reduced HCC incidence in non-cirrhotic patients [29] reported a relatively high HCC incidence in the untreated control group (approximately 3% annually), similar to that reported in cirrhotic patients of other studies; in addition, there were some differences in baseline characteristics between treated and untreated non-cirrhotic patients, indicating that these results may have to be interpreted with caution. Thus, for non-cirrhotic patients, more studies with longer follow-ups are needed to provide conclusive evidence regarding the effect of treatment on HCC.

For patients of Caucasian origin, no comparative study assessing HCC outcomes with and without NA therapy is currently available. One recent US study comparing PS-matched cohorts of treated and untreated cohorts demonstrated an overall risk reduction with anti-HBV therapy of 60%, but the type of NAs used was not specified [60]. A number of single-arm studies assessed HCC outcomes in Caucasian patients treated with entecavir- or tenofovir. Comparing HCC data from these studies (annual rates in non-cirrhotic patients: 0.1–1.0%; cirrhotic patients: 1.5–5.2%) with those previously published in natural history studies (annual rates in non-cirrhotic patients: 0.3%; cirrhotic patients: 2.2% [2]), it appears that in Caucasian patients, NA treatment has little or no impact on HCC reduction in both patients with and without cirrhosis. However, such comparisons need to be interpreted cautiously due to possible differences in patient characteristics between different cohorts (particularly due to inclusion of older patients in the most recent cohorts). More studies with appropriate controls are needed to establish the impact of NA therapy on HCC in patients of Caucasian origin.

When comparing treated patients of different ethnicities, it appeared that annual HCC incidences were comparable between Asian and mixed-ethnicity populations. This is in contrast with previous reports in untreated patients showing 2–3-fold higher HCC rates in Asians [2,61]. However, such comparisons are again difficult because of different patient characteristics, including differences in the criteria for treatment indication and reimbursement.

Regarding the association of virologic suppression and HCC development, conflicting results have been reported. In Asian

studies, achievement of a VR was associated with a lower HCC risk, in particular among patients with cirrhosis; however this could not consistently be confirmed in European studies, which is in agreement with a previous report in Caucasian patients treated with lamivudine [62]. The inconsistency might be explained by differences in the patient population such as HBV genotype distribution. In addition, a difficulty with this type of analysis is the generally small number of patients without virologic suppression and HCC cases during potent antiviral therapy with entecavir or tenofovir. However, it might also be that just the achievement of a VR is not sufficient for reducing HCC risk. For example, it has been reported that the duration of VR to NAs was significantly associated with HCC risk ($\geqslant$24 months: HR = 0.10) [55], whereas other studies found that HCC risk reduction was associated with treatment-induced HBsAg seroclearance [63], or reduction in HBV DNA and qHBsAg levels (HBsAg <100 IU/ml) [64].

The fact that achievement of virologic suppression *per se* is not necessarily associated with a reduced HCC risk may also explain why most studies comparing entecavir or tenofovir with older NAs did not observe a difference in HCC risk reduction between agents. In most of these studies, 30–50% of the lamivudine-treated patients were switched to entecavir or tenofovir. The only report which did observe a significantly greater HCC risk reduction with entecavir than with lamivudine is the study by Hosaka *et al.* [26], where no rescue therapy was used (as it was not available for this historical control cohort). Several studies found that HCC development was significantly associated with resistance development, resistance-associated virologic breakthrough, low genetic barrier drug regimen, and prior lamivudine exposure [37,39,43]. These findings are consistent with earlier results from Liaw *et al.* showing increased disease progression in patients with lamivudine resistance [16], and suggest that incomplete viral suppression that results in resistance and breakthrough-related hepatic flares can be a risk factor for HCC.

Implications for clinical practice and future research

An important message that emerges from this review is that although HCC risk can be reduced with the current NAs entecavir and tenofovir, it cannot be eliminated (at least within several years of therapy) due to risk factors that are not amenable to change by antiviral therapy (such as family history of HCC, duration of the infection, or HBV genotype), or carcinogenic events that may have taken place before treatment initiation (such as prior treatment exposure and history, or integration of HBV DNA into the host genome). Thus, HCC surveillance remains an important component in the management of treated patients, even if they maintain complete viral suppression. This is the context in which valid HCC risk calculators may be useful. The tools available today partially fulfill such goals to the extent that variables that are not modifiable by antiviral therapy can be identified. In Asian patients, the REVEAL, CU-HCC, and GAG-HCC risk calculators have been shown to be valid in one cohort of Asian patients treated with entecavir [53]. A revised version of REACH-B, incorporating liver stiffness values (by transient elastography) instead of serum HBV DNA, has been shown to accurately predict liver-related events among patients that achieve a complete VR under NA treatment [65]. For Caucasian patients receiving antiviral therapy, particularly entecavir or tenofovir, the PAGE-B score appears to be the most suitable HCC risk predictor [49]. Additional validated pre- and on-therapy calculators derived from other patient populations would be of great practical value to inform best practice for HCC surveillance and to facilitate patient counseling. HCC risk scores may also be used to complement treatment indications as recommended by current CHB practice guidelines. For example, some patients whose HBV DNA levels indicate an increased HCC risk based on HCC scores may not be recommended for antiviral therapy by the guidelines. In addition, qHBsAg levels, which have been shown to correlate with HCC risk in some patients [13], may be integrated into HCC risk prediction and patient management [66].

Another important point is that all of the observational data discussed in this review, as well as the data from the Liaw *et al.* trial [16], were derived from a subset of CHB patients, namely those who have evidence of active liver disease, and are at risk of progression and future complications based on CHB treatment guidelines. Therefore, the data in this review should not be construed to indicate that HCC risk may be reduced in all patients with HBV infection. For example, there has been no study to date assessing the effect of antivirals on HCC risk in patients in the immune-tolerant phase, or in HBeAg-negative patients with normal ALT but elevated HBV DNA levels.

In summary, accumulating evidence indicates that antiviral therapy with the current NAs entecavir or tenofovir prescribed to control hepatic inflammation and prevent or reverse liver fibrosis can also reduce the risk of HCC, especially in Asian patients. Further studies are needed to describe the impact of treatment in non-cirrhotic patients, and in patients of Caucasian ethnicity. Additional studies may also be justified to investigate whether there are subgroups of patients who currently do not meet the treatment criteria, and yet may benefit from HCC risk reduction by being treated with potent antiviral agents. Other future research opportunities may include mechanistic studies to understand cellular processes in which antiviral therapy may interfere with carcinogenesis. They may inform the search for biomarkers and clinical predictors of response, ultimately leading to individualized management of HBV patients to optimize clinical benefits of antiviral therapy in reducing the risk of HCC as well as preventing and reversing chronic liver disease.

Conflict of interest

The authors disclose the following: George V. Papatheodoridis: Served as an advisor and lecturer for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Roche as well as a member of the Data Safety Management Board for clinical trials of Gilead, and has received research grants from Bristol-Myers Squibb, Gilead, and Roche. Henry Lik-Yuen Chan: Served as a consultant and speaker for Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, Novartis, and Roche, has received honoraria for lectures from AbbVie, GlaxoSmithKline, and Echosens, and has received an unrestricted grant for research in hepatitis B from Roche. Bettina Hansen: No conflict of interest. Harry Janssen: Received consulting/research support from Roche, Merck, Gilead, Bristol-Myers Squibb, Novartis, Santaris, Medtronic, Anadys, Innogenetics, and Kirin. Pietro Lampertico: Served on advisory boards and speaker bureaus for Bristol-Myers Squibb, Roche, Gilead, and GlaxoSmithKline.

Authors' contributions

All authors were involved in the selection and interpretation of the included data, drafting of the manuscript, and critical revision of the manuscript for intellectual content. This review in its entirety is the work of the authors alone; they selected the data to be included, drafted and reviewed the manuscript, and decided on the overall conclusion of the manuscript.

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Supplementary data

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