We identified six cohort studies with large sample sizes which fulfilled our inclusion criteria.\textsuperscript{3-8} Participants of one study were from Hong Kong,\textsuperscript{3} and those of the other four studies were from Korea.\textsuperscript{4,6-8} The last cohort study analyzed an international consortium that encompassed 19 centres from six countries or regions (United States, n = 5; China, n = 3; Hong Kong, n = 2; Japan, n = 4; South Korea, n = 1; Taiwan, n = 4).\textsuperscript{5} Therefore, most of the participants were of Asian origin. All these six retrospective cohort studies composed of treatment-naïve CHB patients treated with either TDF or entecavir monotherapy.\textsuperscript{3-8} The follow-up duration ranged from 32.0 to 69.9 months. The overall incidence rate of HCC was 3.20% (581/18157) in TDF group and 5.24% (2523/48130) in entecavir group. Subgroup analysis in propensity score matching analysis found that the incidence rate of HCC was 3.35% (524/15645) and 5.40% (845/15645) in the corresponding groups. Pooled results revealed that CHB patients treated with TDF monotherapy showed a statistically significant lower rate of HCC occurrence compared to entecavir monotherapy as a whole (RR 0.46, 95% CI 0.33-0.66, \textit{P} < 0.001) or after propensity score matching analysis (RR 0.53, 95% CI 0.36-0.76, \textit{P} < 0.001). The results were consistent with that of sensitivity analyses based on the fixed-effect or random-effect model, or excluded one study one by one.

In conclusion, this meta-analysis revealed that TDF was superior to entecavir monotherapy for HCC prevention in CHB.

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LINKED CONTENT

This article is linked to Brancaccio et al and Yip and Wong papers. To view these articles, visit https://doi.org/10.1111//apt.15188 and https://doi.org/10.1111//apt.15614.

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on-treatment hepatitis B virus DNA suppression and alanine aminotransferase normalisation, which are associated with favourable clinical outcomes. Among CHB patients with cirrhosis, both entecavir and TDF reduce disease progression, HCC development and mortality. However, after the initial publication by Choi et al, which showed a difference in TDF vs entecavir on HCC prevention using a Korean nationwide cohort, debate has ensued about the possible difference between the two anti-viral agents. The debate was escalated after studies suggested no difference from other centres, including those in Korea, the country of Choi’s study. Using a territory-wide cohort in Hong Kong, our group showed similar results to those of Choi et al.

Currently, studies were able to compare entecavir and TDF on long-term clinical outcomes since both agents have been registered and prescribed to patients for a sufficiently long time. An issue that is yet to be covered is that TDF is associated with impairment of renal function in some patients. Therefore, TDF-treated patients with deteriorating renal function may be switched to tenofovir alafenamide (TAF), which has a better renal and bone safety profile. Treatment-naive patients might also be considered for TAF if necessary. As long-term data on the use of TAF emerge in the coming years, we expect new studies comparing the effectiveness of entecavir, TDF and TAF on long-term outcomes including HCC among CHB patients with possibly changing risk profile due to ageing and other changing contributable factors including metabolic syndromes.

However, we must be alert when interpreting meta-analyses of non-randomised cohort studies. Although all studies rigorously adjusted for confounding bias, each could possibly have unmeasured confounding. Ignoring these biases from each of the non-randomised studies and summarising them directly may add up to serious unmeasurable and unpredictable bias. The inclusion of duplicated patients from studies (ie study using Korean nationwide cohort and other studies using Korean hospital cohorts) further complicates the interpretation of results. Moreover, the follow-up duration for entecavir and TDF treatment groups were usually different in the non-randomised cohort studies due to the delayed availability of TDF after entecavir. Ignoring the difference in follow-up duration and comparing the two groups by risk ratio could introduce time bias.

In conclusion, whether TDF-treated patients have a lower risk of HCC than entecavir-treated patients remains uncertain. This controversy may continue to evolve as we anticipate further high-quality cohort studies for analysis.

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