Role of Antivirals in the Prevention of Hepatocellular Carcinoma in Patients with Chronic Hepatitis

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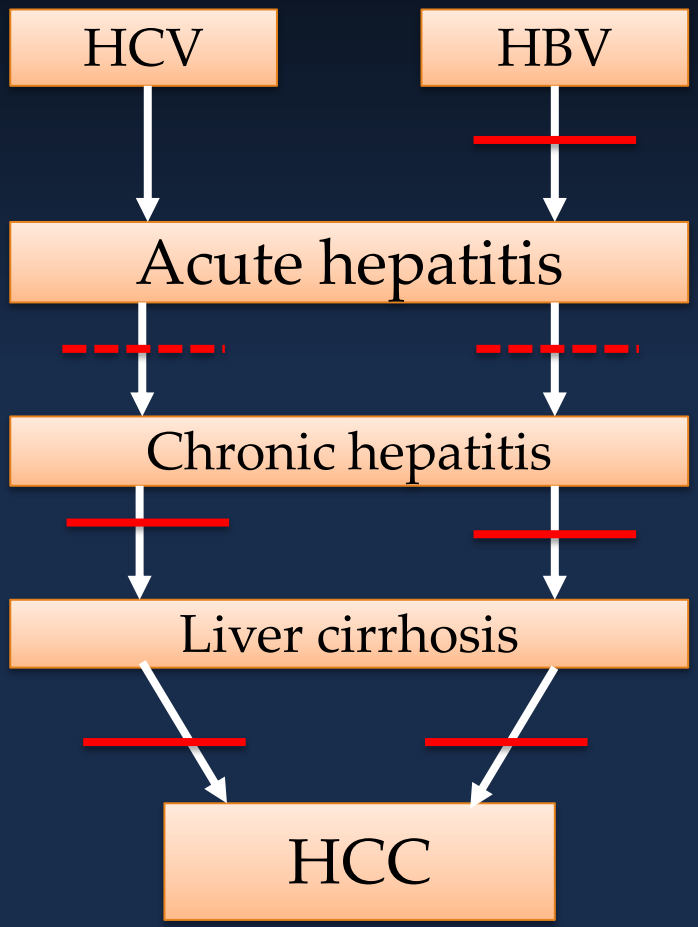
Background

- Approximately 75% of HCC worldwide are attributed to chronic hepatitis B (CHB) and chronic hepatitis C (CHC).
- Most of them occur in cirrhotic liver
- The advent of potent oral antivirals has shown their efficacy to reduce viral load.
- Does antivirals prevent HCC in patients with chronic hepatitis B and C ?

Strategies to Prevent HCC



Vaccine, only available for HBV

Antiviral therapy:

- in non-cirrhosis
- in cirrhosis

Lok AS. J Gastroenterol Hepatol 2011; 26:221-7.

Hepatitis B vs. Hepatitis C

HEPATITIS B

- DNA virus
- Viral genome replicate in the nuclei
- Primary treatment goal: SUSTAINED HBV SUPPRESSION[1]

HEPATITIS C

- RNA virus
- Viral genome replicate in the cytoplasm
- Primary treatment goal: ERADICATION OF HCV[2]

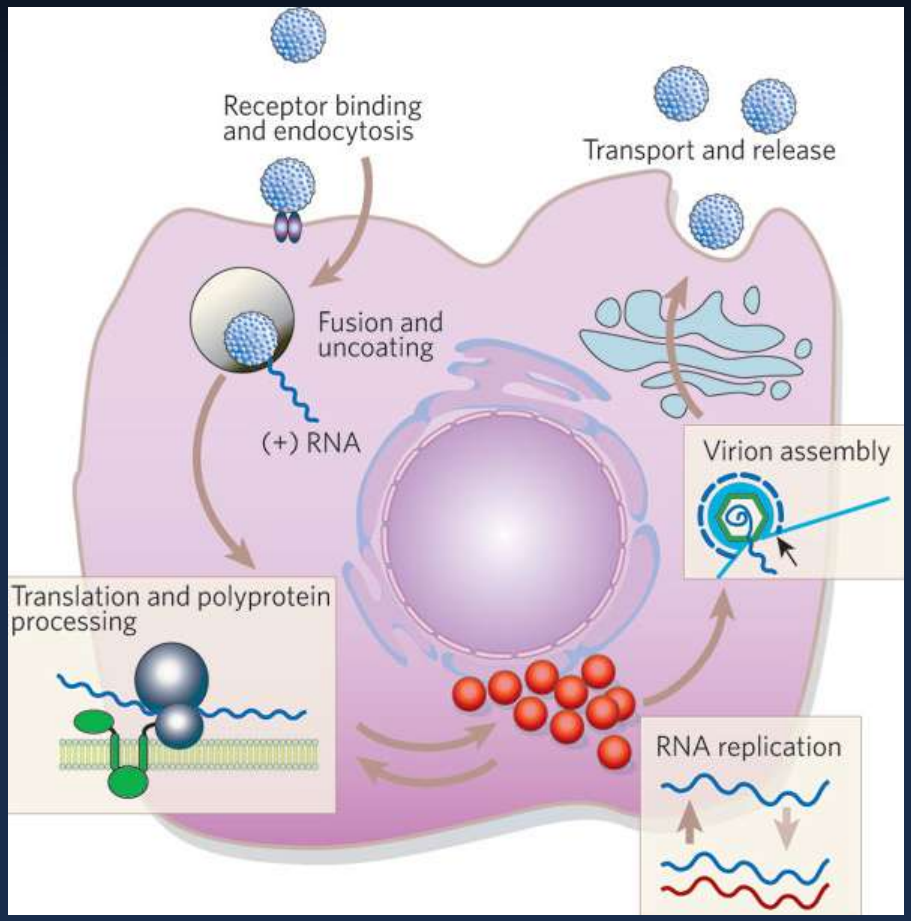
1. Lai CL, Yuen MF. N Engl J Med 2008;359-2488-90.

HCV life cycle

1. Entry into the cell and uncoating;
2. Translation, replication, and packaging into new virion

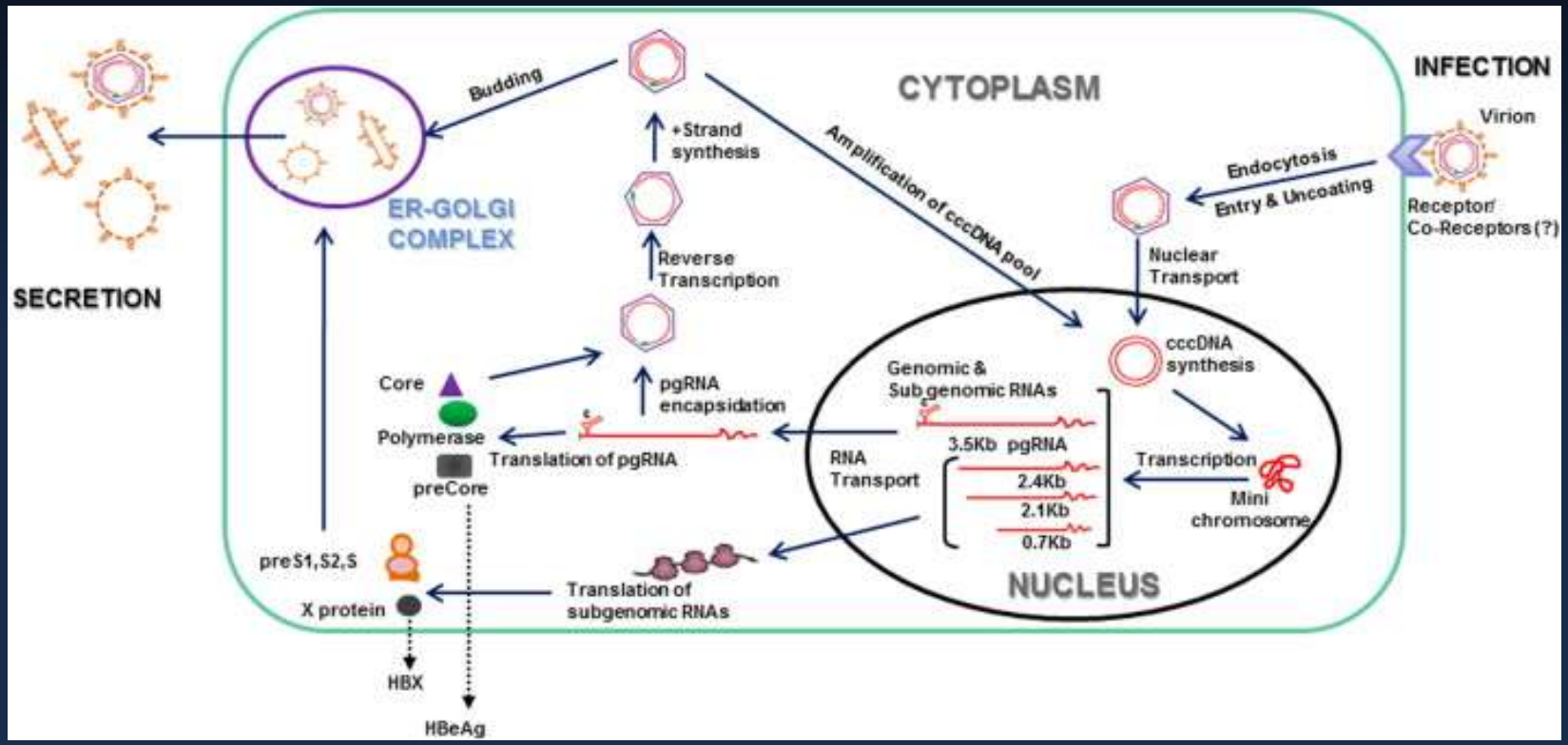
All occur in the cytoplasm

Eradication is POSSIBLE



Lindenbach BD, Rice CM. Nature 2005;436:933-8.

HBV life cycle



Following entry and uncoating, HBV genome enter the nucleus to replicate.

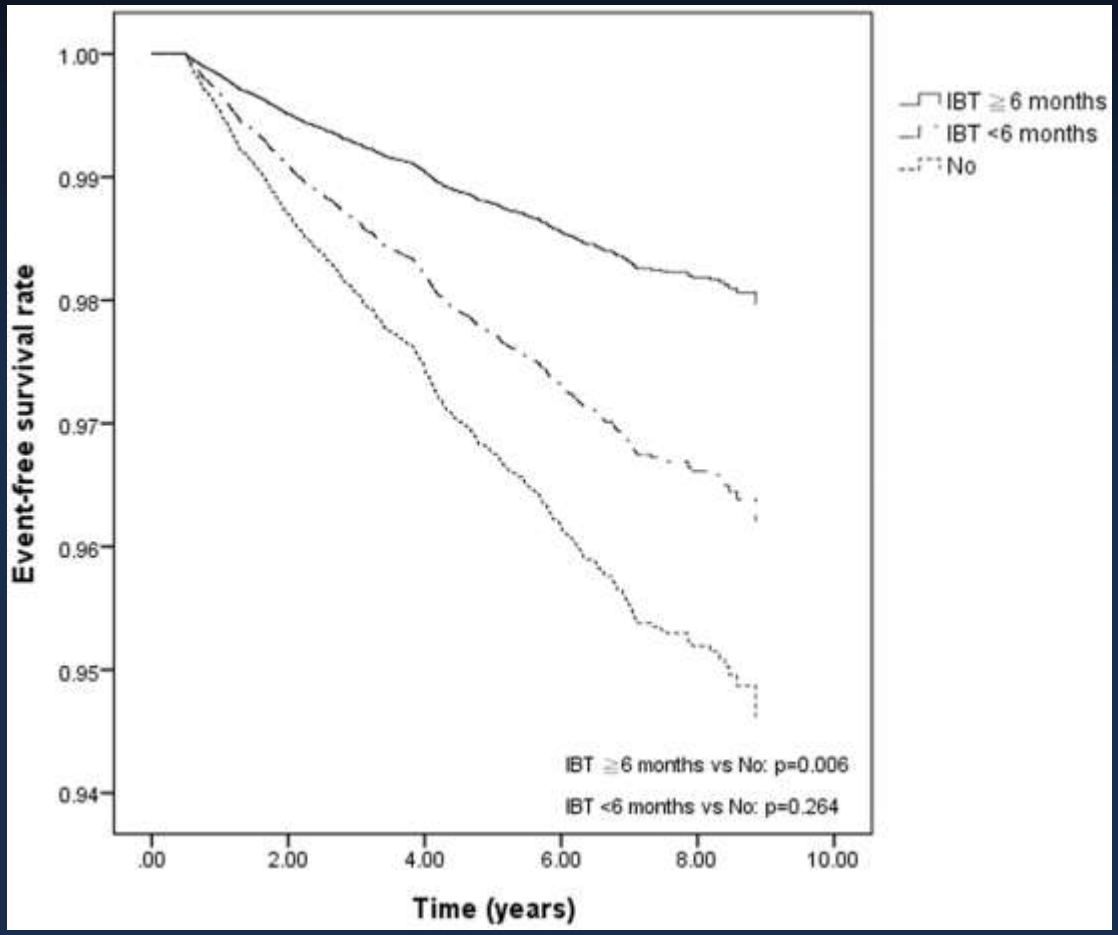
ERADICATION IS IMPOSSIBLE

Datta S, et al. J Clin Exp Hepatol. 2012;2:353-65.

Antiviral treatment for HCC prevention

CHRONIC HEPATITIS C

HCC-free survival rate by IFN



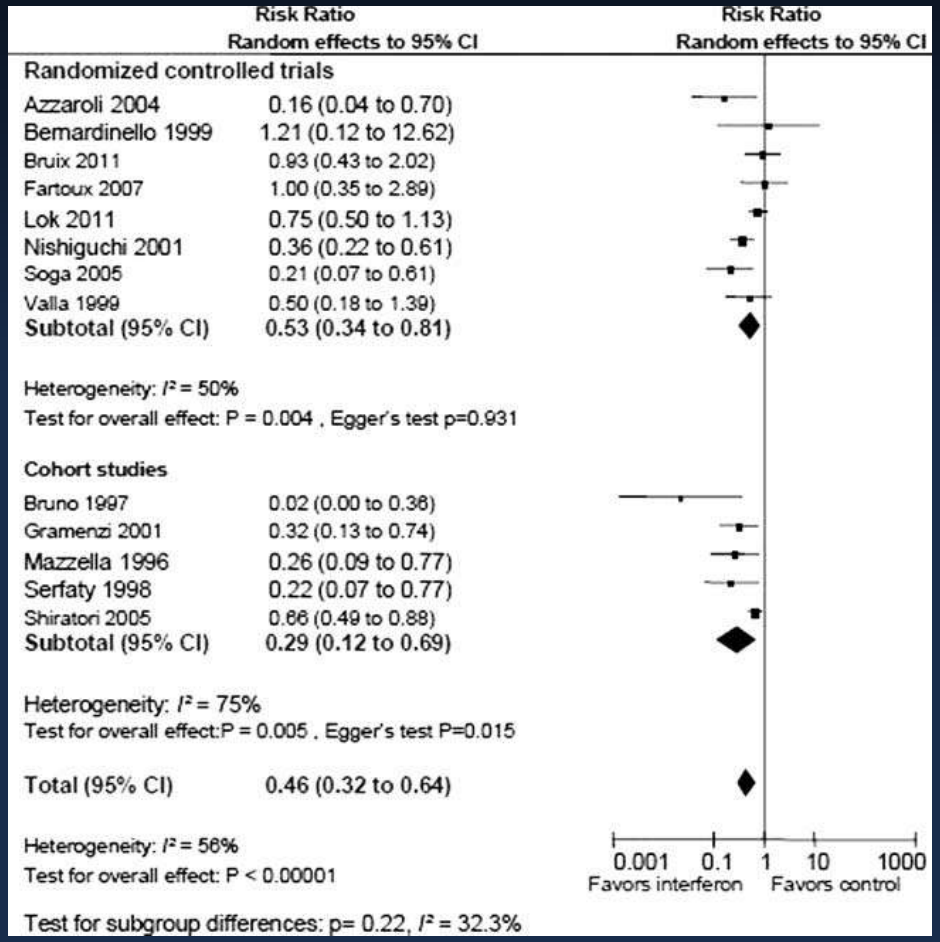
IFN-based treatment reduces HCC risk in chronic hepatitis C patients

IBT = Interferon-based treatment

Hsu CS, et al. PloS ONE 2013;8(7):e70458. doi:10.1371/journal.pone.0070458

Meta-analysis of antiviral therapy to prevent HCC in CHC

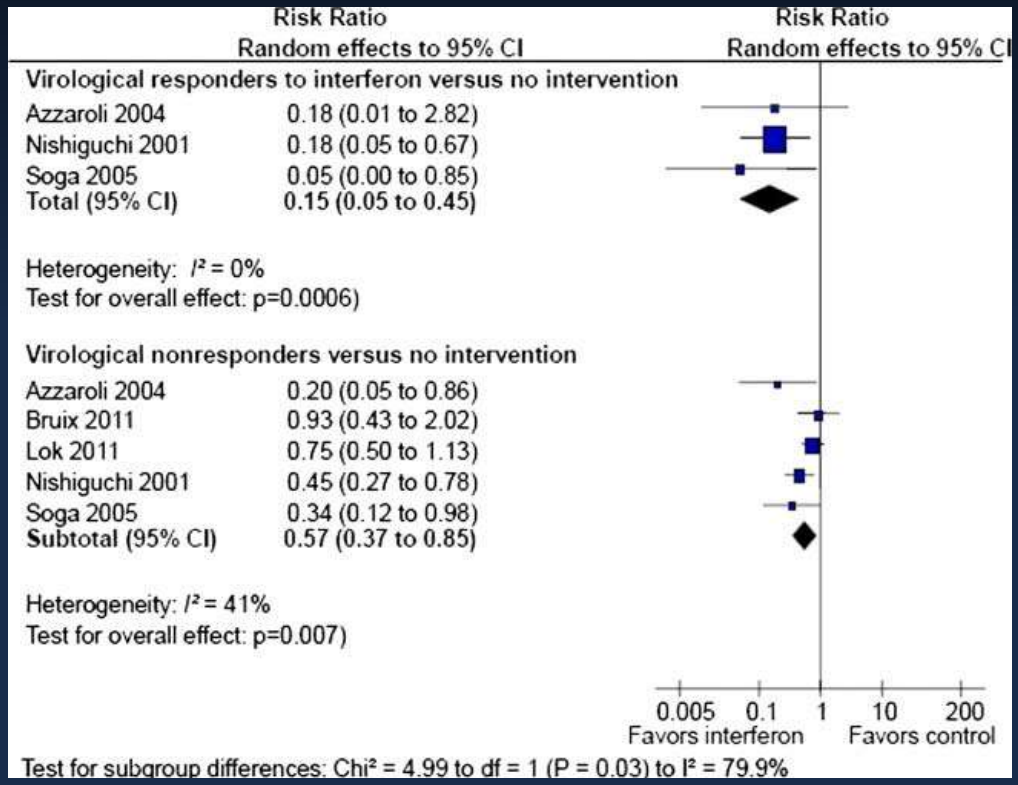
- 8 RCTS and 5 cohort studies;
- antiviral therapy reduced the risk of HCC (RR 0.53, 95% CI 0.34 to 0.81)



Kimer N, et al. BMJ Open 2012;2:e001313. doi:10.1136/bmjopen-2012-001313.

Responders vs. non-responders

- Subgroup analysis:
- the effect was more pronounced among responders (RR 0.15, 95% CI 0.05 to 0.45) compared with non-responders (RR 0.57; 95% CI 0.37 to 0.85).

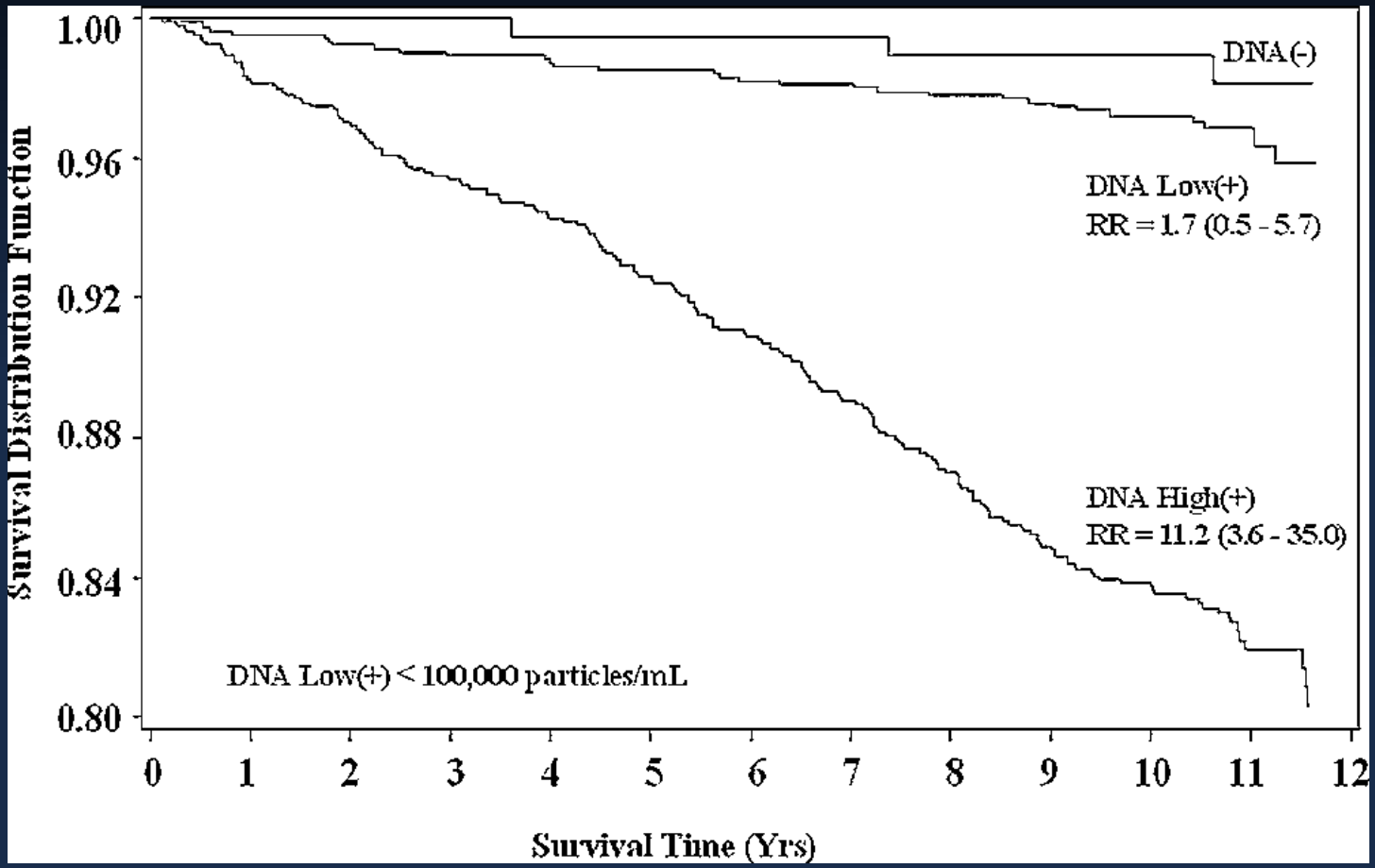


Kimer N, et al. BMJ Open 2012;2:e001313. doi:10.1136/bmjopen-2012-001313.

Antiviral treatment for HCC prevention

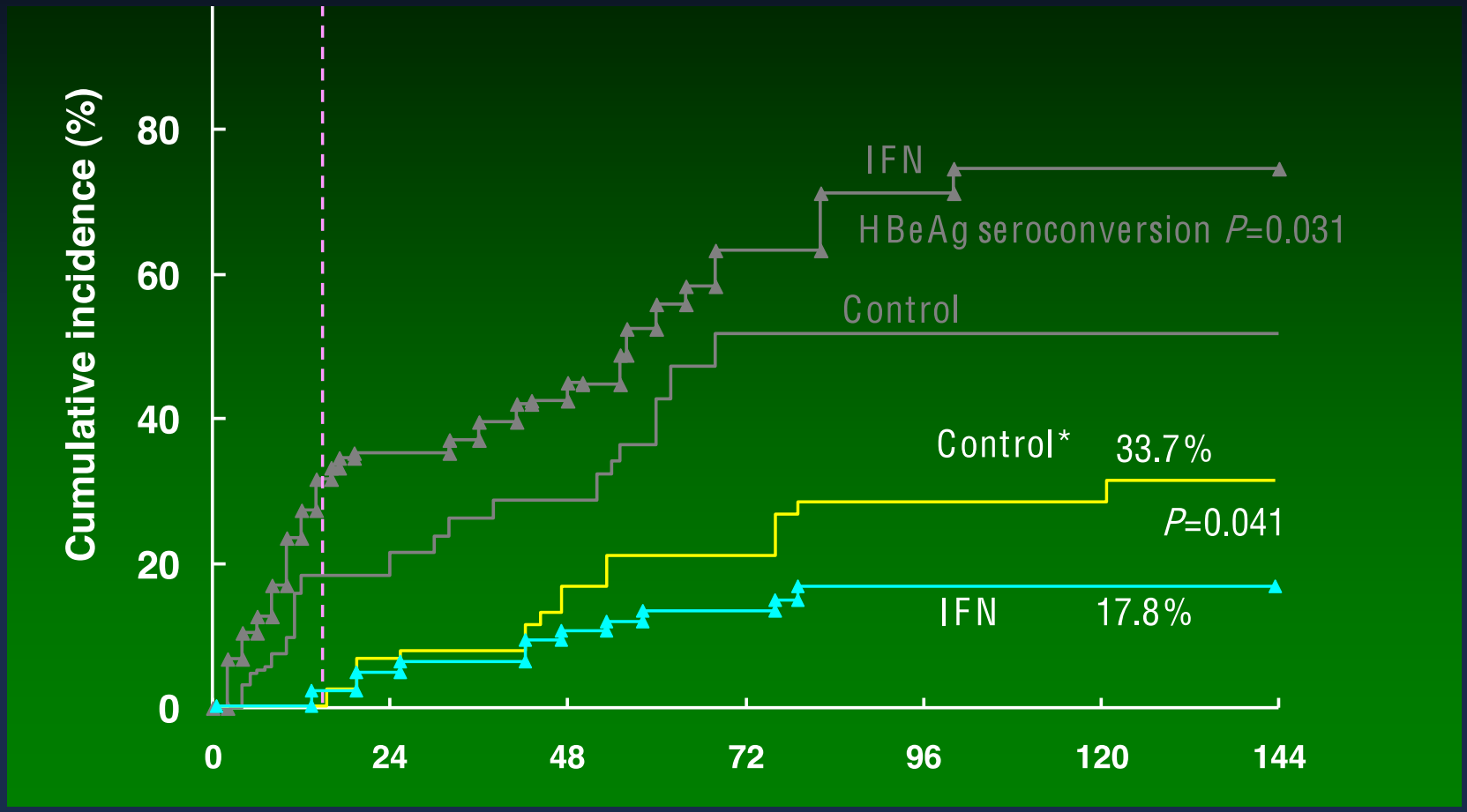
CHRONIC HEPATITIS B

HCC risk and mortality in CHB is related to the viral load



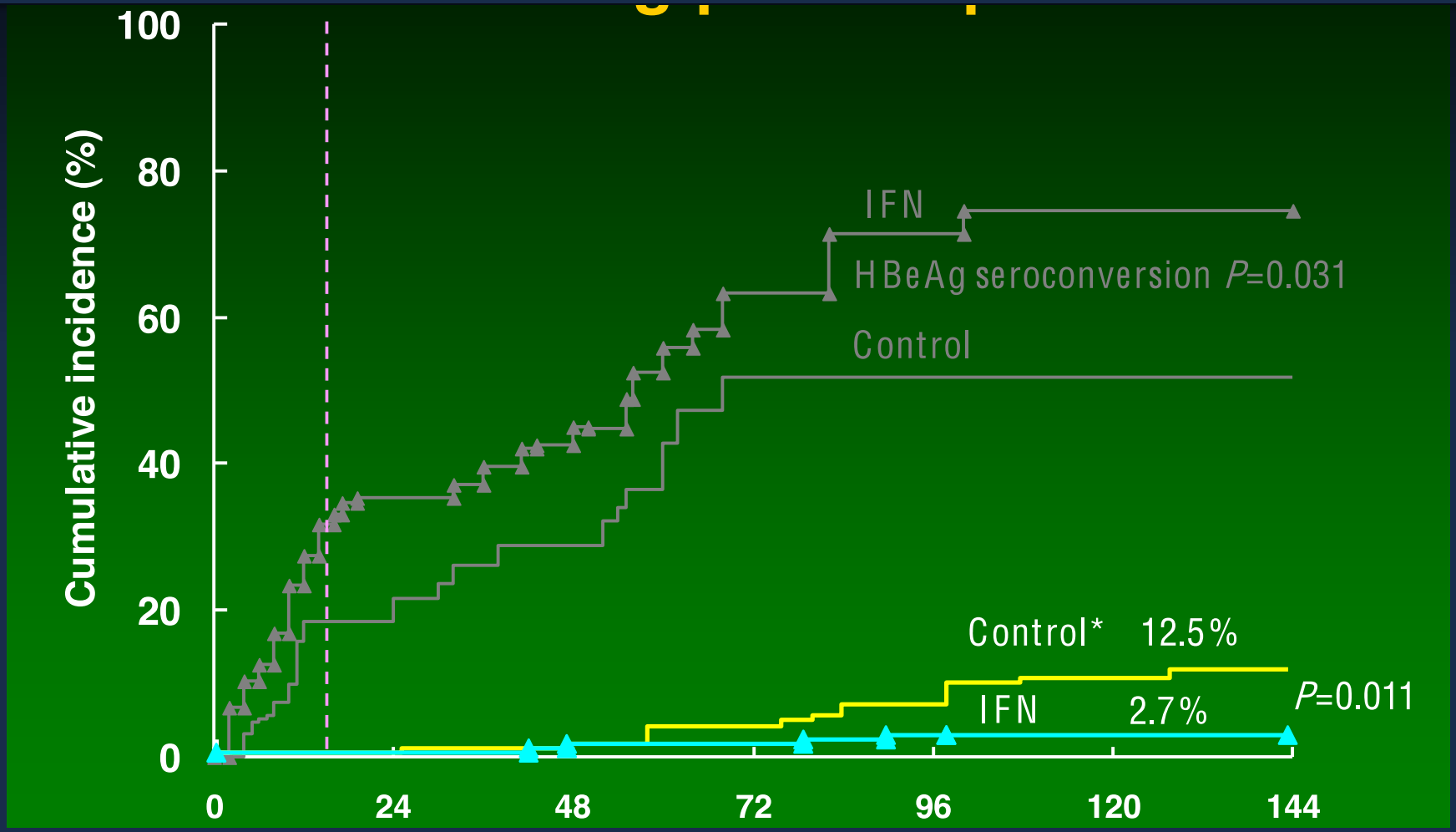
Chen G, et al. Am J Gastroenterol 2006;101:1797-803.

IFNα reduced cirrhosis in HBeAg-positive patients



Lin SM, etl al. J Hepatol. 2007;46:45-52.

IFNα reduced HCC in HBeAg-positive patients



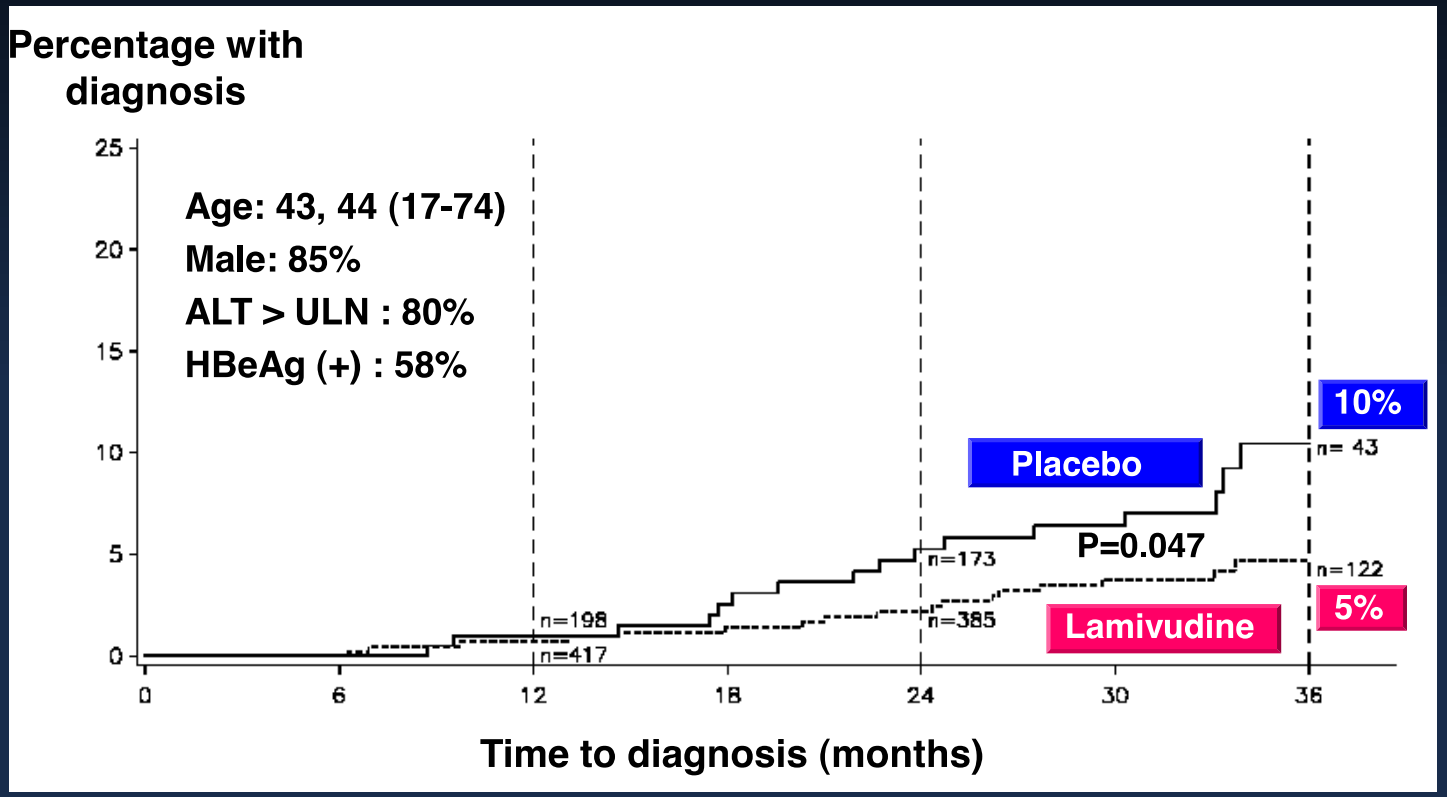
Lin SM, etl al. J Hepatol. 2007;46:45-52.

LAM treatment and HCC

- LAM treatment (median: 43 months) reduces HCC incidence by more than 50%
- 9.7% per year in untreated controls vs. 3.3% per year in LAM-treated patients.
- LAM therapy is associated with a 56% reduction in the incidence of HCC among chronic HBV patients compared with no treatment.

Liaw YF, et al. N Engl J Med 2004; 351: 1521-31.

Reduction of HCC with LAM in patients with advanced fibrosis/cirrhosis

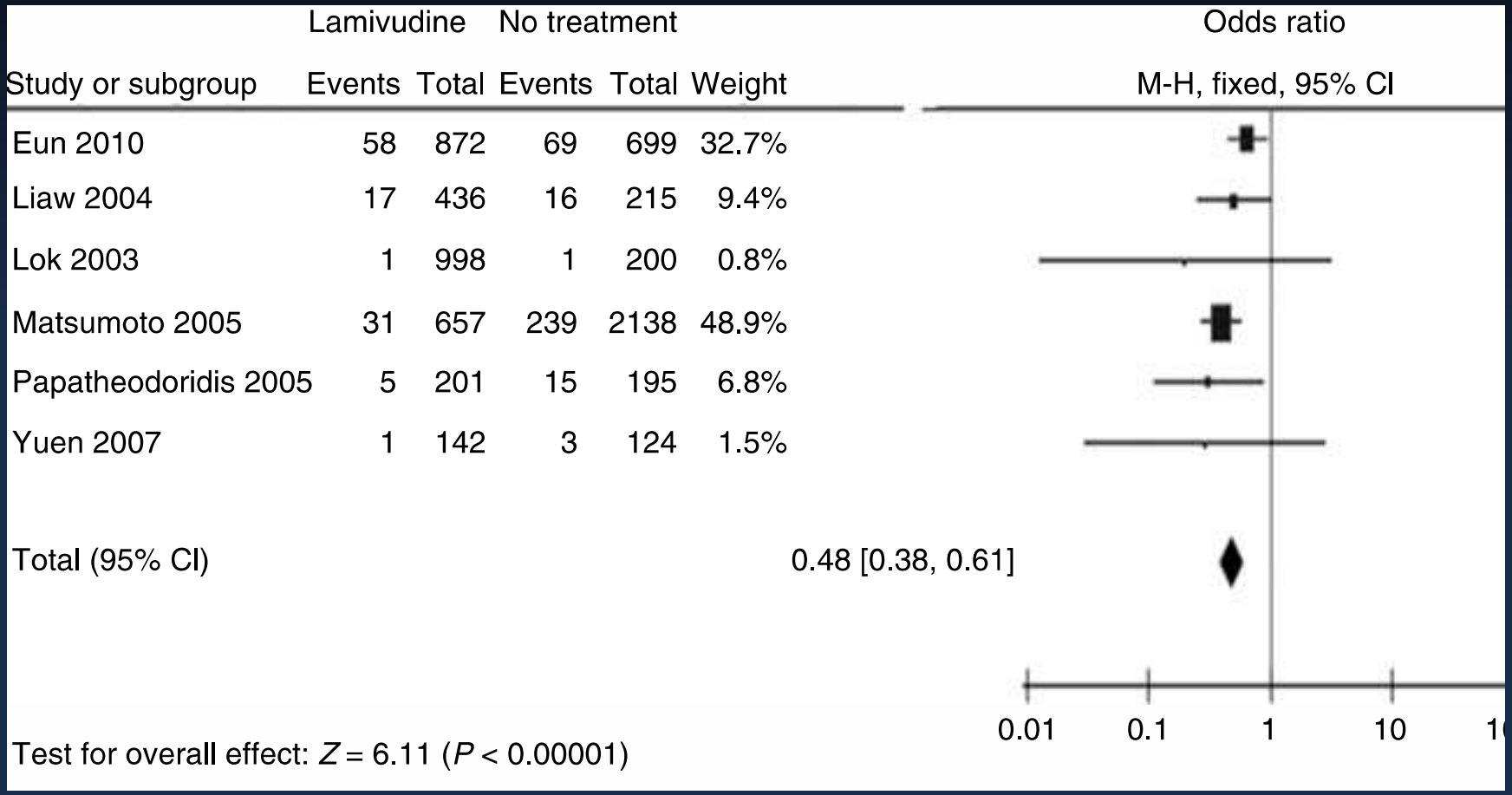


Placebo (n=215)
Lamivudine (n=436) / 32.4 mo

Excluding 5 cases in yr 1: HR=0.47; p=0.052

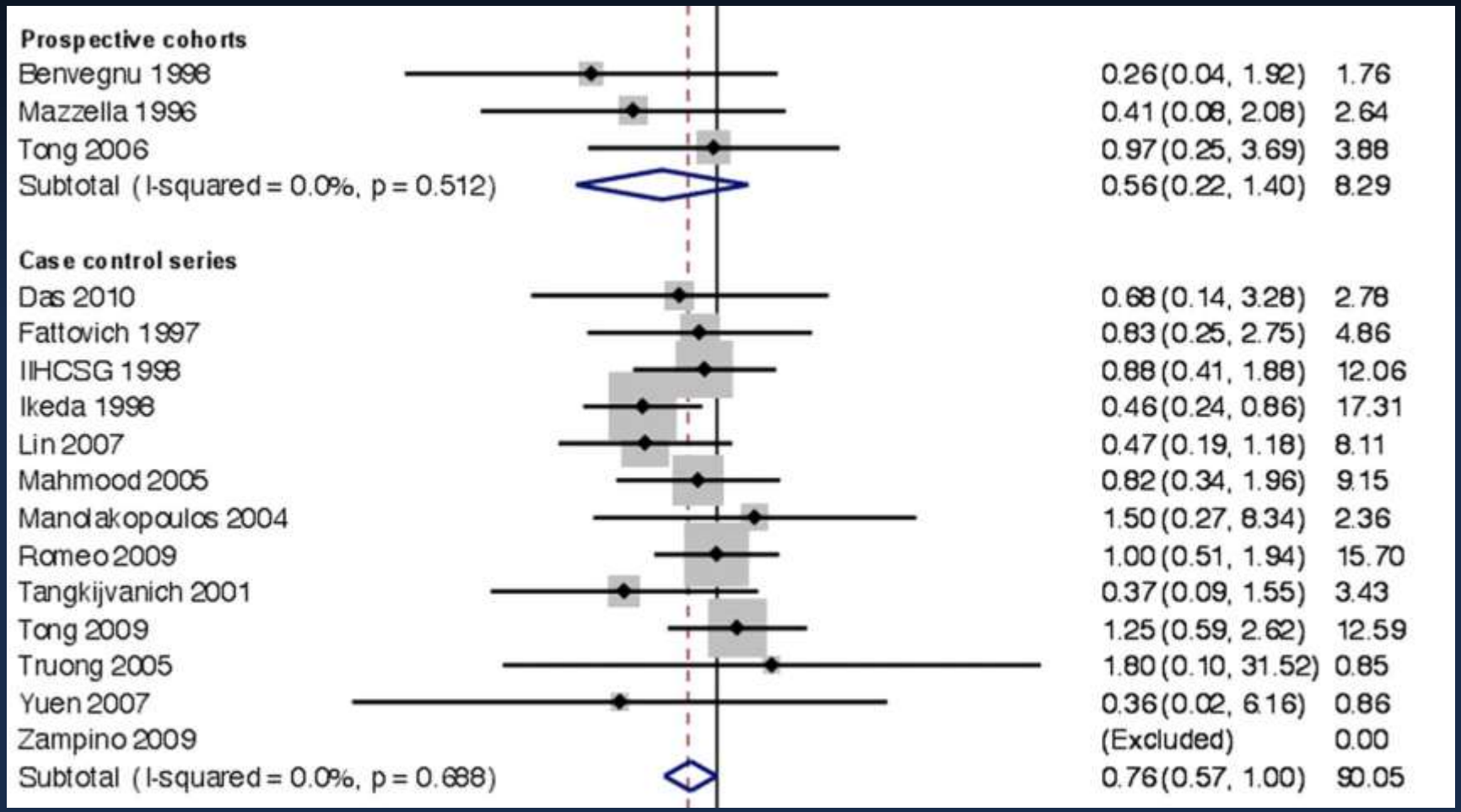
Liaw YF, et al. N Engl J Med 2004; 351: 1521-31.

Meta-Analysis of LAM on HCC incidence in CHB



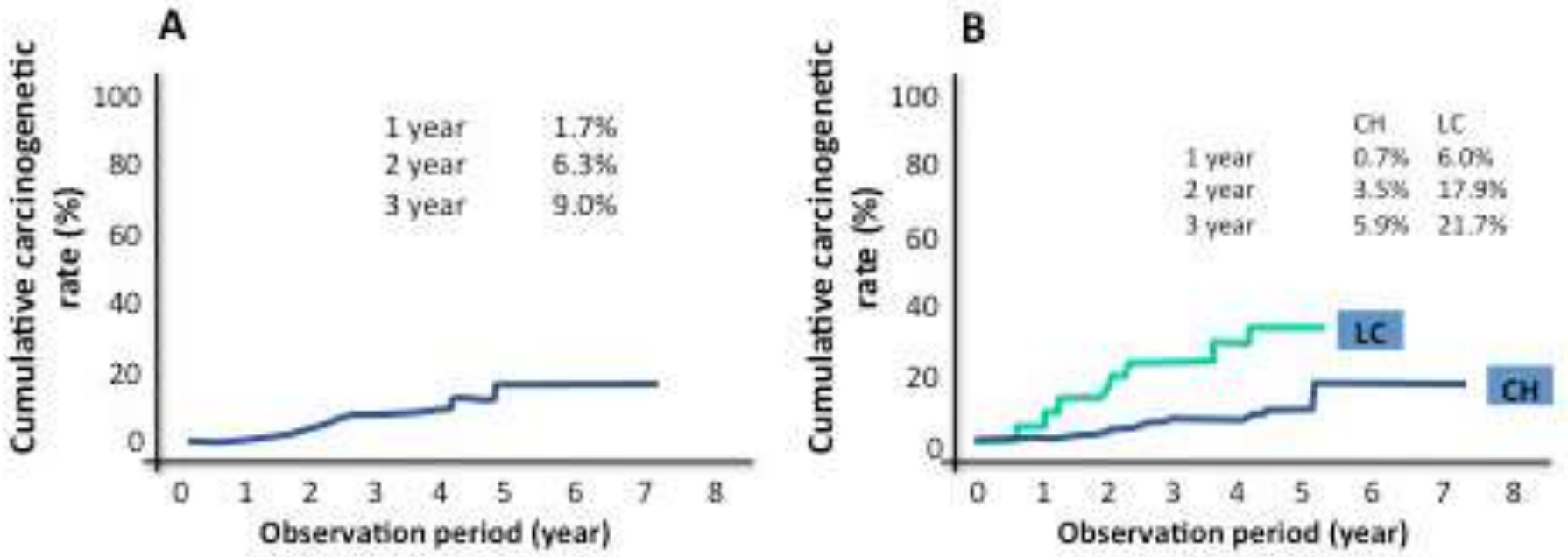
Singal AK, et al. Aliment Pharmacol Ther 2013;38:98-106.

Meta-Analysis of Antiviral Therapy on HCC Risk in CHB



Thiele M, et al. BMJ Open 2013;3:e003265

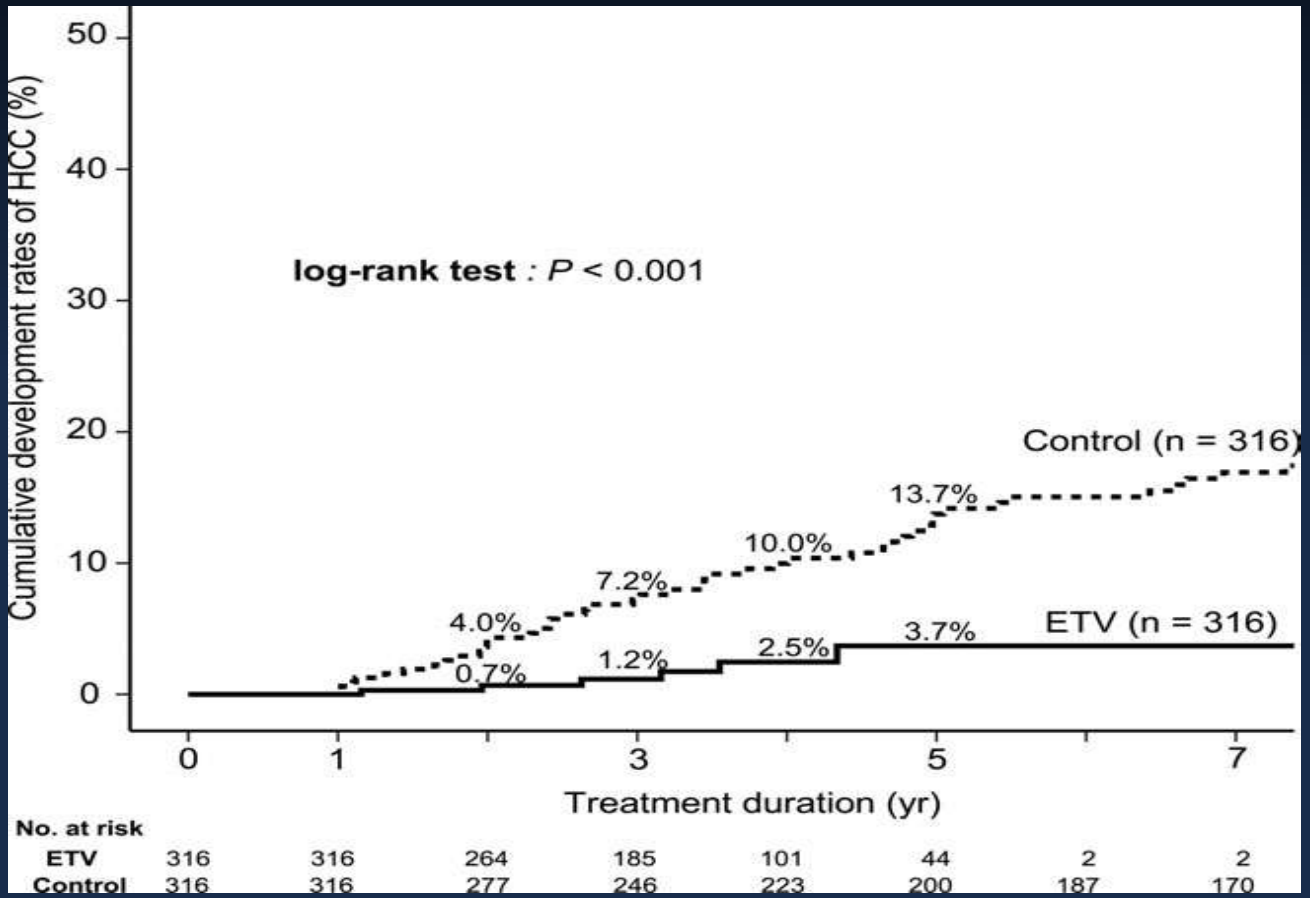
Cumulative carcinogenic rate during ETV treatment A: A patients B: patients stratified with chronic hepatitis (CH) and liver cirrhosis (LC).



cumulative carcinogenic rates were much higher in cirrhotic patients

AASLD 2012. Poster presentation by Ryoko Yamada.

Long-term entecavir (ETV) reduces HCC in HBV infection



Hosaka T, et al. Hepatology 2013;58:98-107.

Table 1 Risk factors for hepatitis B virus-related hepatocellular carcinoma

Host factors	Liver factors	Viral factors
Advanced age	Advanced fibrosis	High serum HBV DNA
Male gender	Cirrhosis	Positive HBeAg
Family history of HCC	Hypoalbuminemia	HBV genotype C
SNP at human genomic loci, *e.g.*	Hyperbilirubinemia	HBV subgenotype Ce
Chromosome 1p36.22	High ALT	Core promoter mutations
Chromosome 6 of HLA-DP/Q loci	Active necroinflammation	High serum HBsAg level
Chromosome 8p12	Concomitant liver diseases, *e.g.*	
Immunosuppressed condition, *e.g.*	Hepatitis C virus co-infection	
Human immunodeficiency virus co-infection	Hepatitis delta virus co-infection	
	Alcoholic liver disease	
	Nonalcoholic fatty liver disease	

Wong GLH, Wong VWS.
World J Gastroenterol 2013; 19(39): 6515-6522

Cirrhosis vs. Non-cirrhosis

- Suppression of viral replication in HBV cirrhosis patients reduces but does not eliminate HCC risk.

- Suppression of viral replication in non-cirrhosis also reduces the risk of HCC, but since the risk of HCC is not as high as in cirrhosis patients, the magnitude of the risk reduction is less.

Sherman M. Hepatology 2013;58:18-20.

Conclusion

- Antiviral therapy may prevent HCC by slowing progression of liver disease and possibly even reversing liver damage.
- Standard treatment of chronic hepatitis C may eliminate HCV and reduce the incidence of HCC.
- Risk reduction is more prominent in treatment responders.
- Treatment with potent antiviral therapy for chronic hepatitis B may suppress viral load and possibly prevent HCC.
- Greatest risk reduction occur in cirrhotic compared to non-cirrhotic patients

Thank you