CU Medicine HONG KONG

HBV related HCC: The role of antiviral therapy in its prevention and management – ETV real world experience

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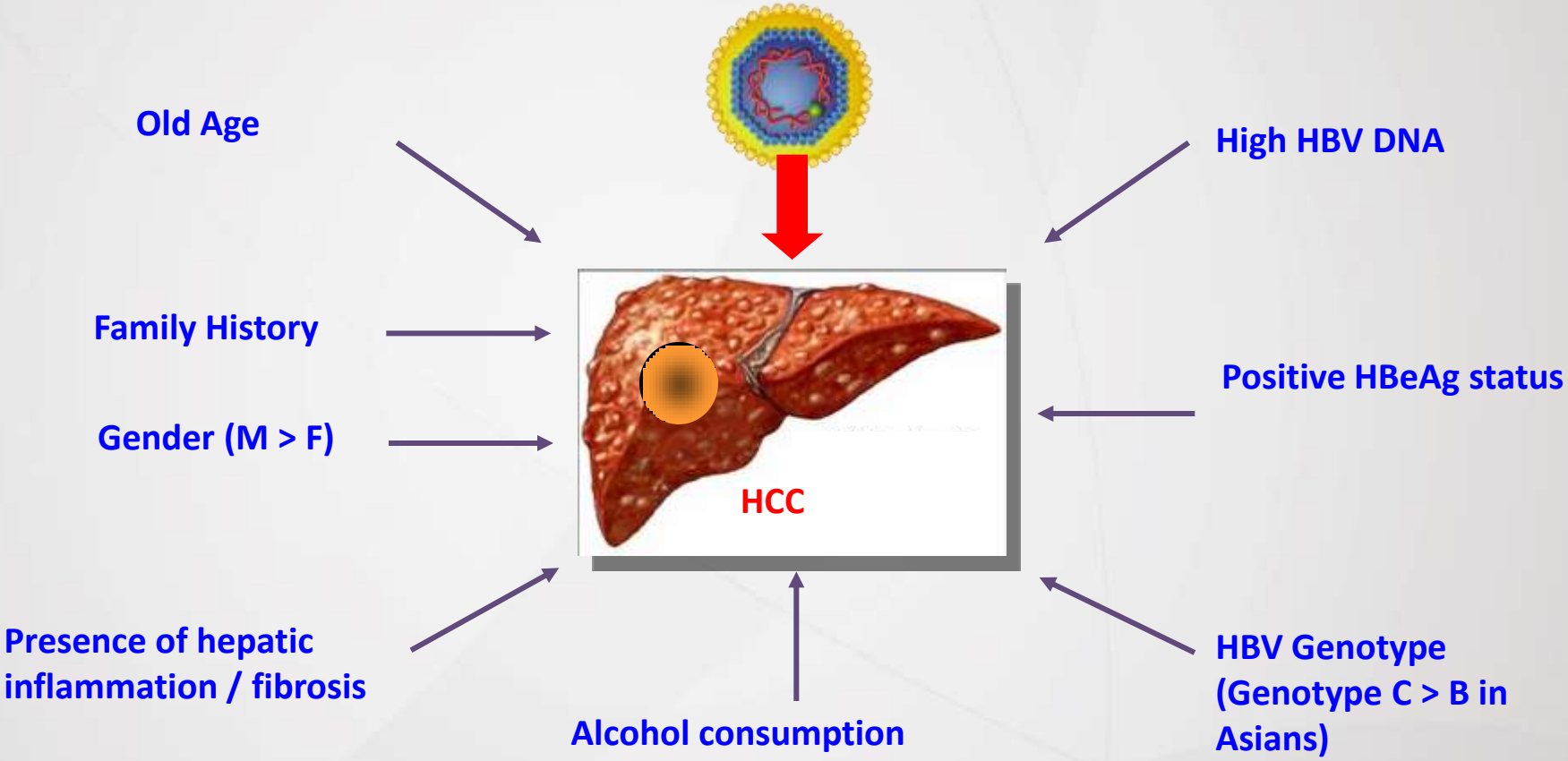
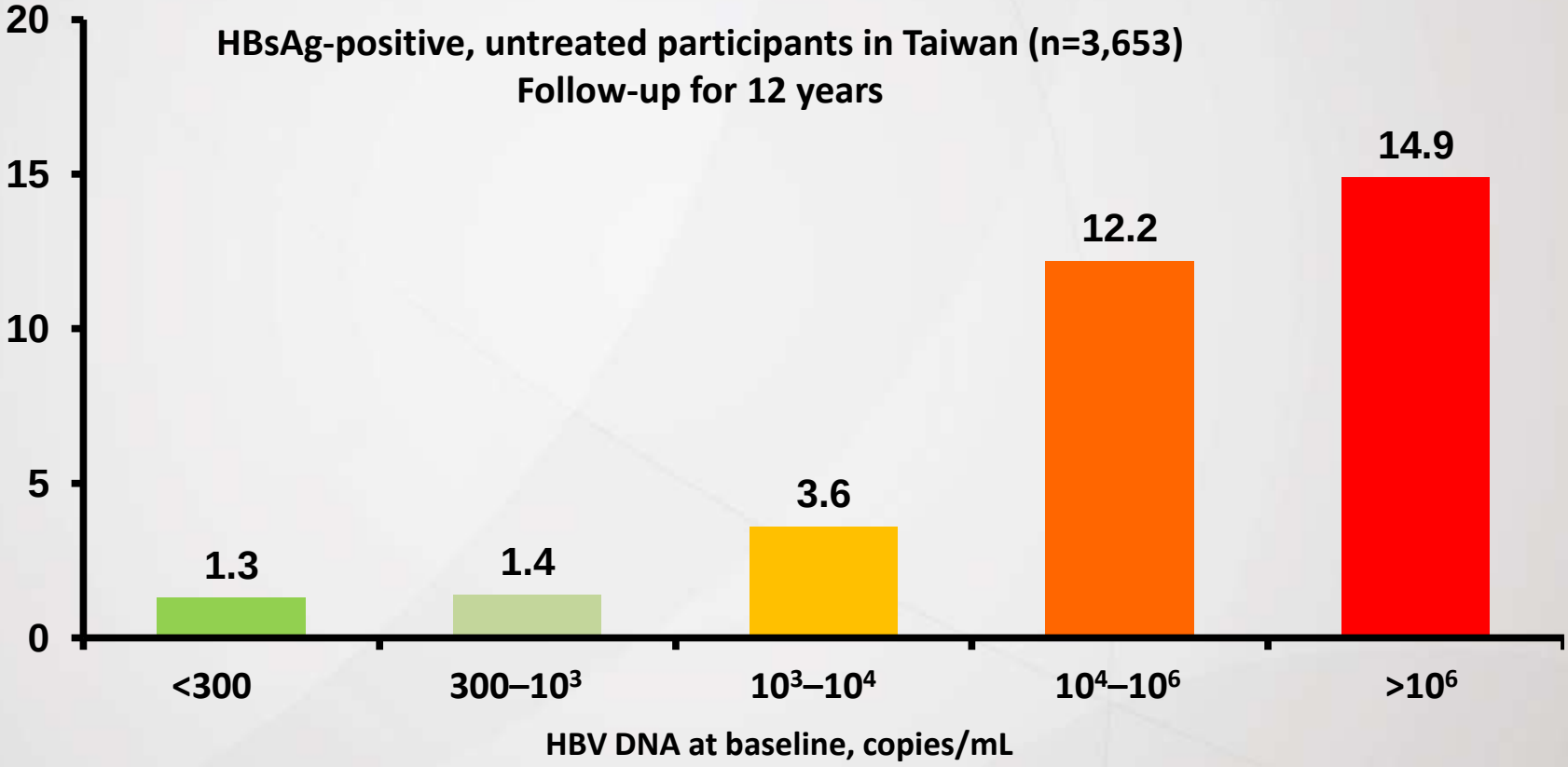
Risk factors of HBV-related HCC



Fattovich G. *Semin Liver Dis* 2003;23:47-58; Chen CJ, *et al*. *JAMA* 2006;295:65-73; Iloeje UH, *et al*. *Gastroenterology* 2006;130:678-86; Chen CJ *J. Gastroenterol Hepatol* 1997;12:S294-S308; Yang HI *et al*. *NEJM* 2002;347:168-174; Yang HI et al. *JNCI* 2008;100:1134-43

Higher HBV DNA is associated with a higher risk of HCC



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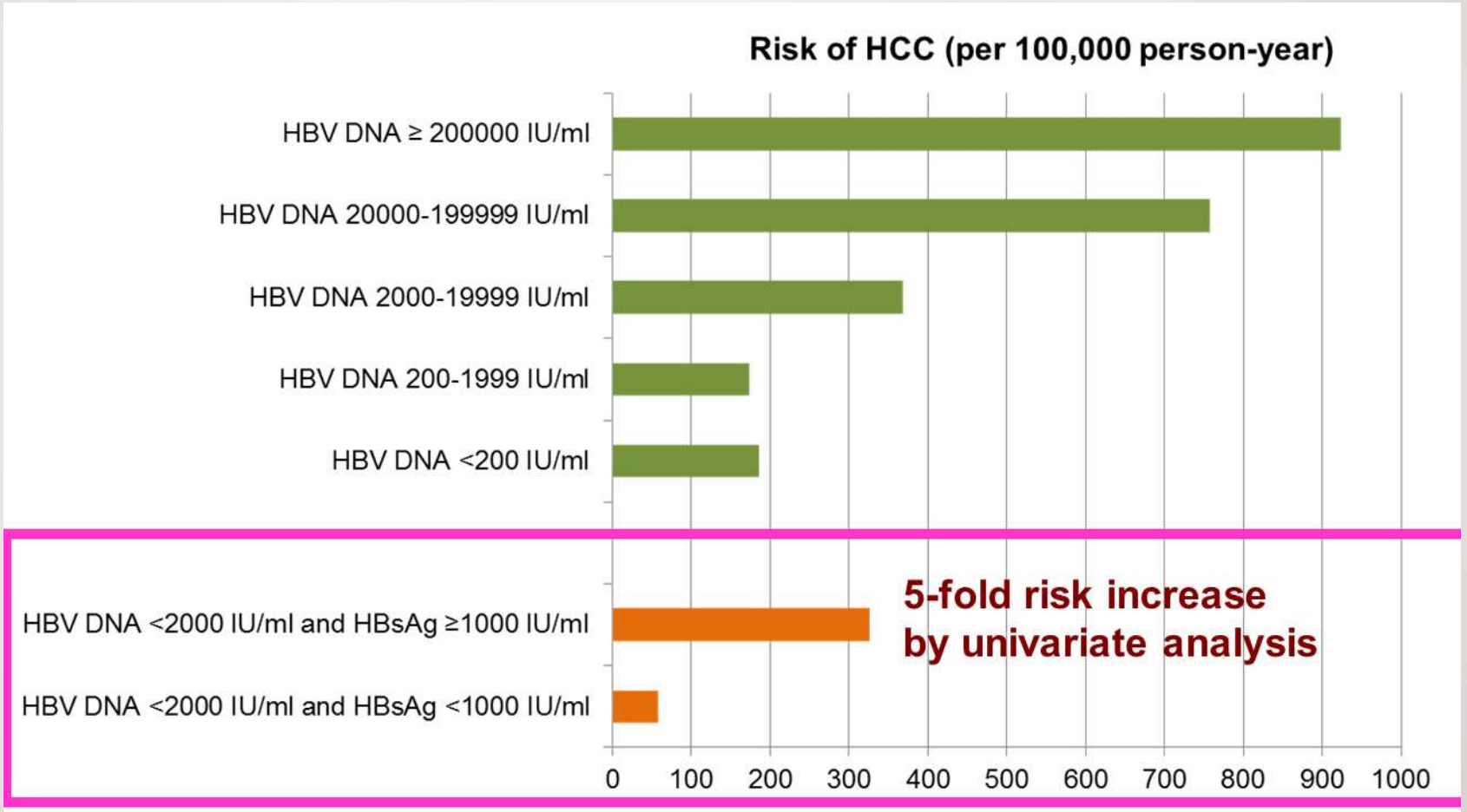
Chen CJ, et al JAMA 2006

HBsAg level is an important risk factor in patients with low HBV DNA level (<2000 IU/mL)

ERADICATE-B (2688 HBV carriers)



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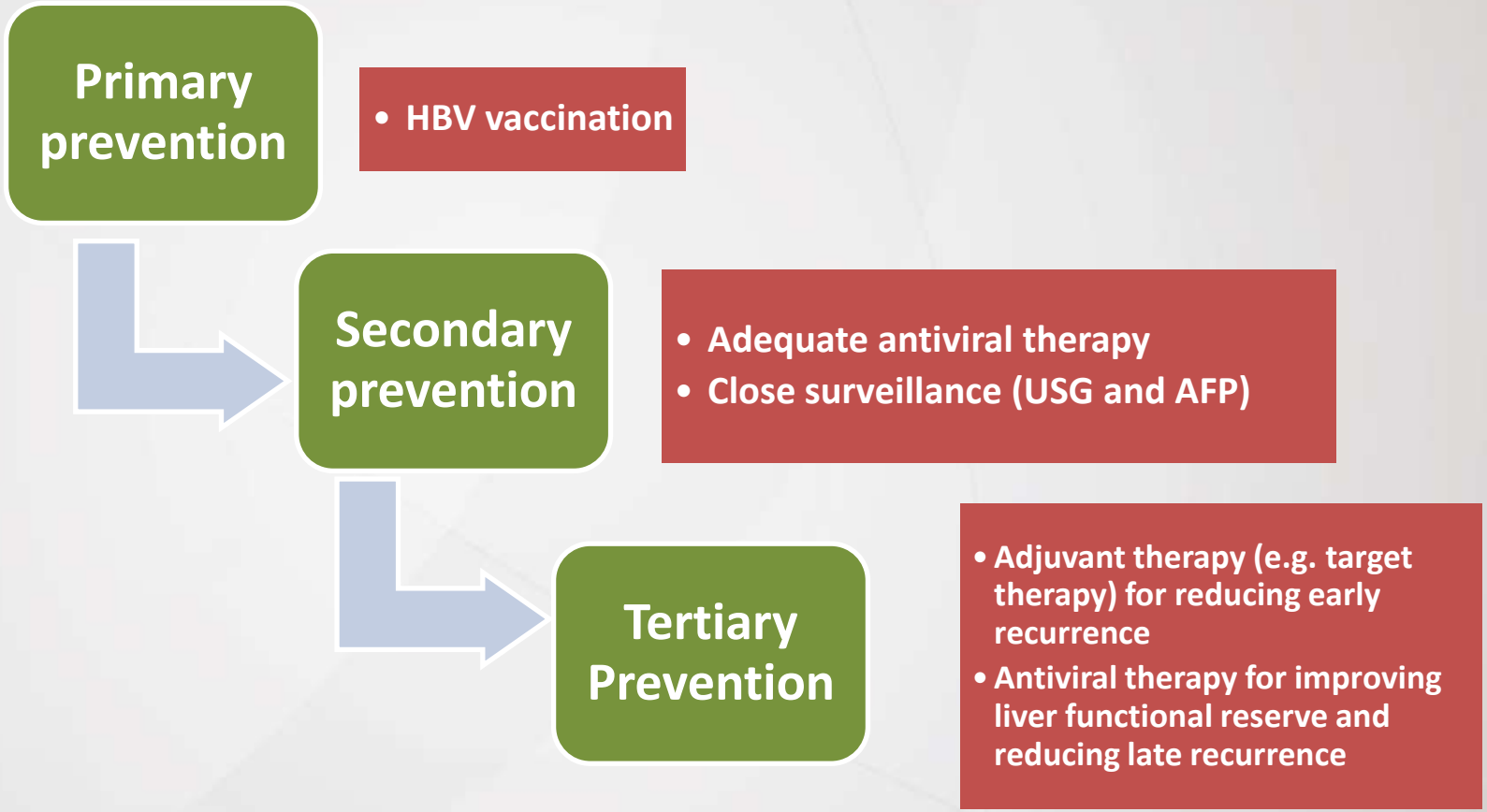
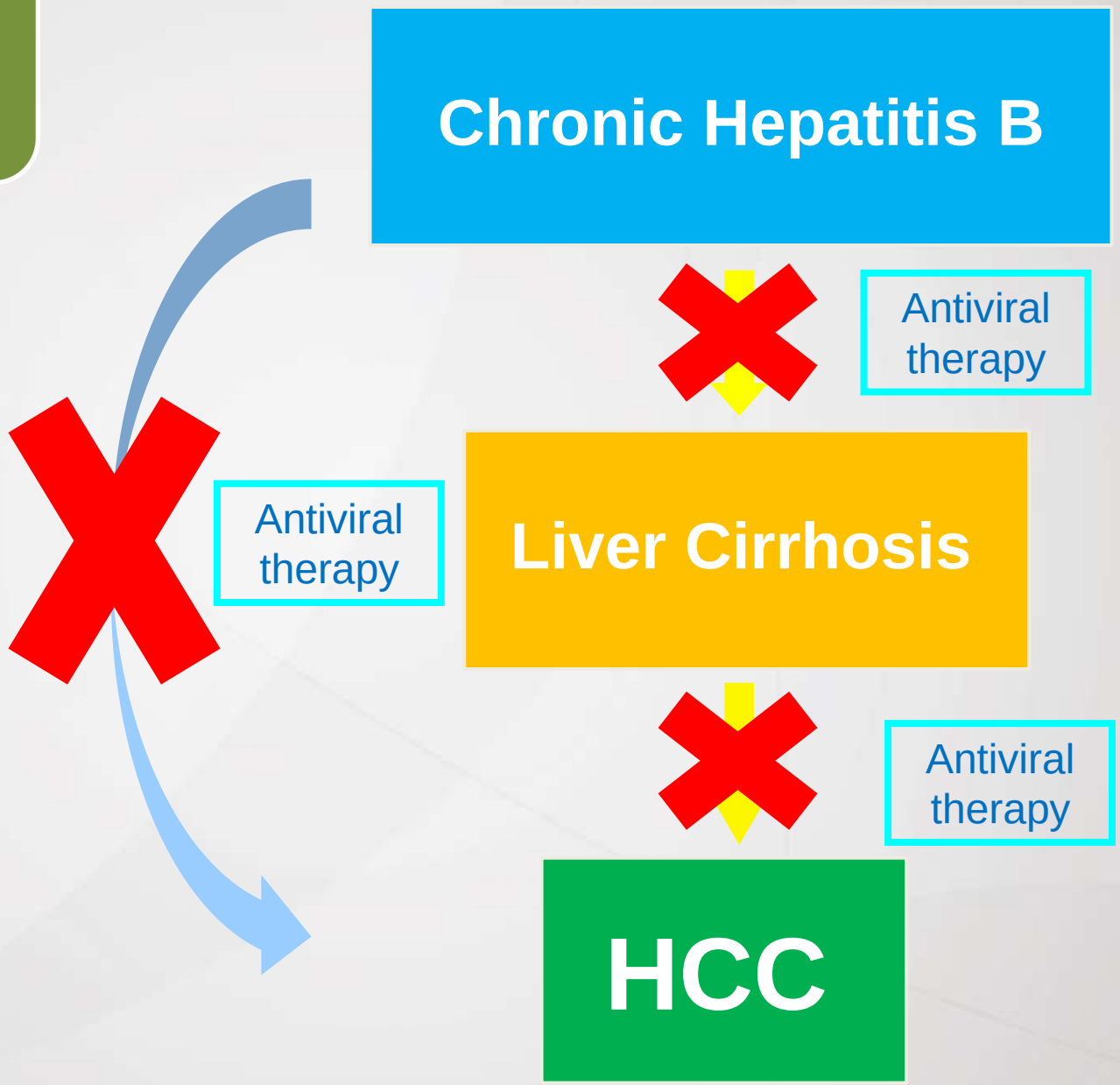
Tseng, Kao. Gastroenterology 2012;
Chan HL. Gastroenterology 2012

Strategies for Preventing HBV-HCC



Secondary prevention



Prevention and management of HBV-related HCC

- Before HCC occurs……
  - Does antiviral therapy prevent HCC occurrence?
  - Who will develop HCC even on antiviral?
  - What is the effect of antiviral on tumor marker?

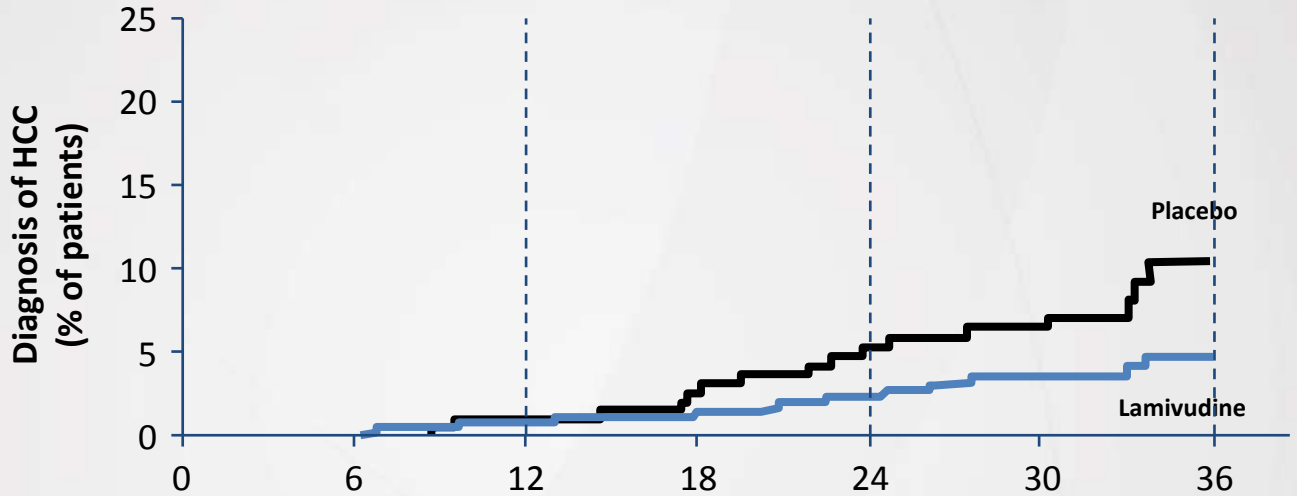
- After HCC occurs……
  - Does high HBV DNA level increase HCC recurrence?
  - Does antiviral therapy prevent HCC recurrence?

Before HCC occurs……

DOES ANTIVIRAL THERAPY PREVENT HCC OCCURRENCE?

Antiviral therapy alters the natural history of chronic hepatitis B

Reduced risk of HCC by lamivudine



No. At risk							
Placebo	215	209	198	184	173	153	43
Lamivudine	436	429	417	400	385	347	122

HCC occurred in 3.9% of lamuvidine-treated group, versus 7.4% of the placebo group (HR=0.47; p=0.047)

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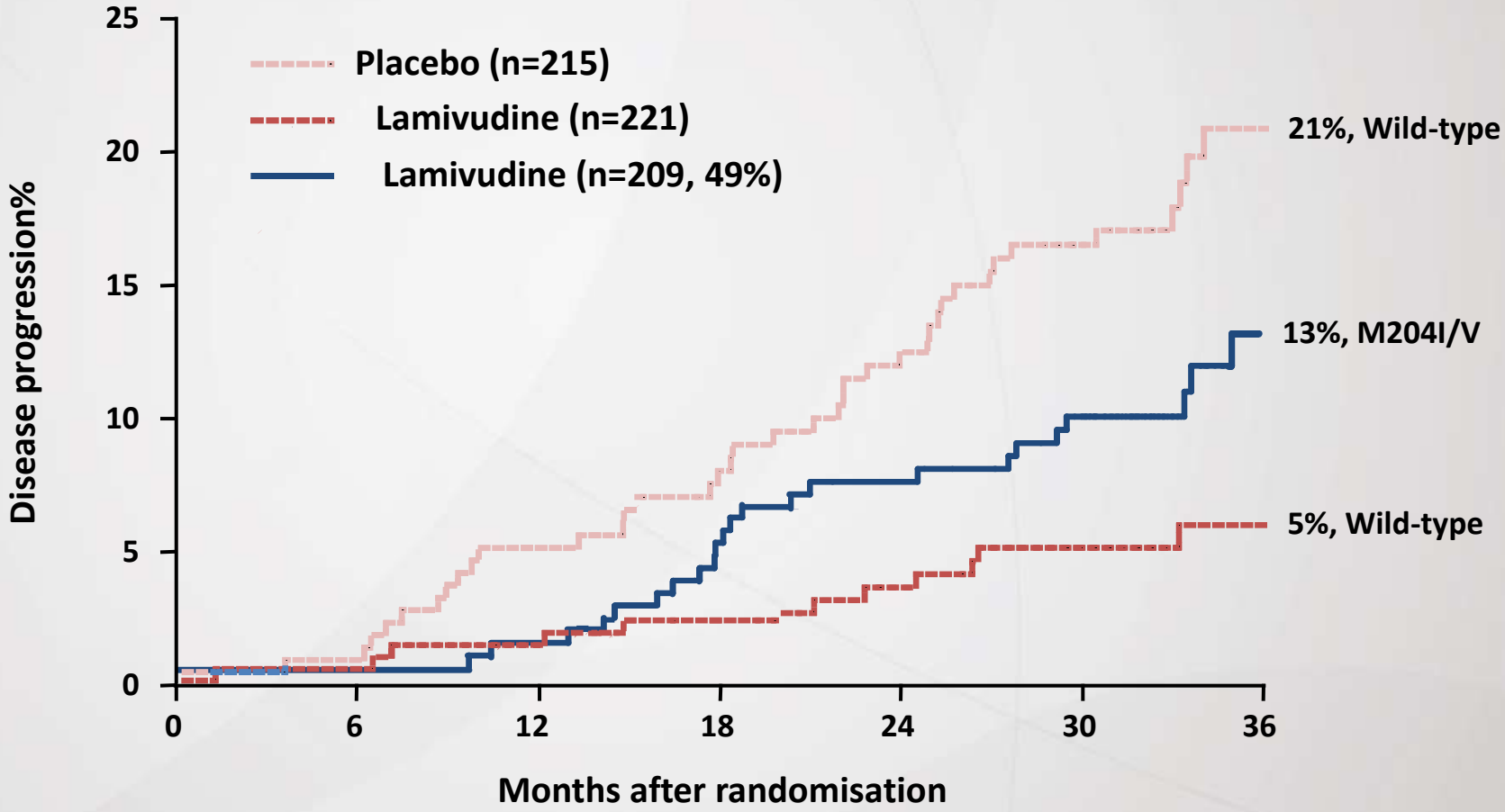
Liaw YF, Sung JJ et al. NEJM 2004

Benefits of lamivudine and issue of drug resistance



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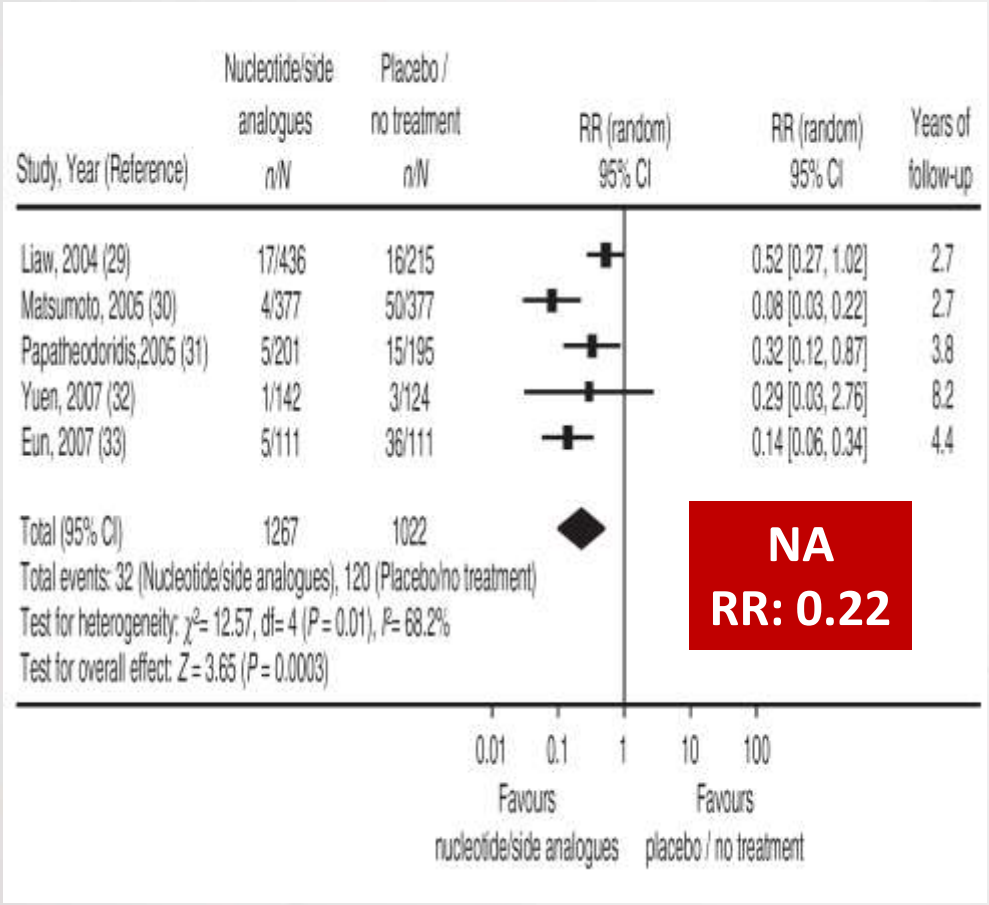
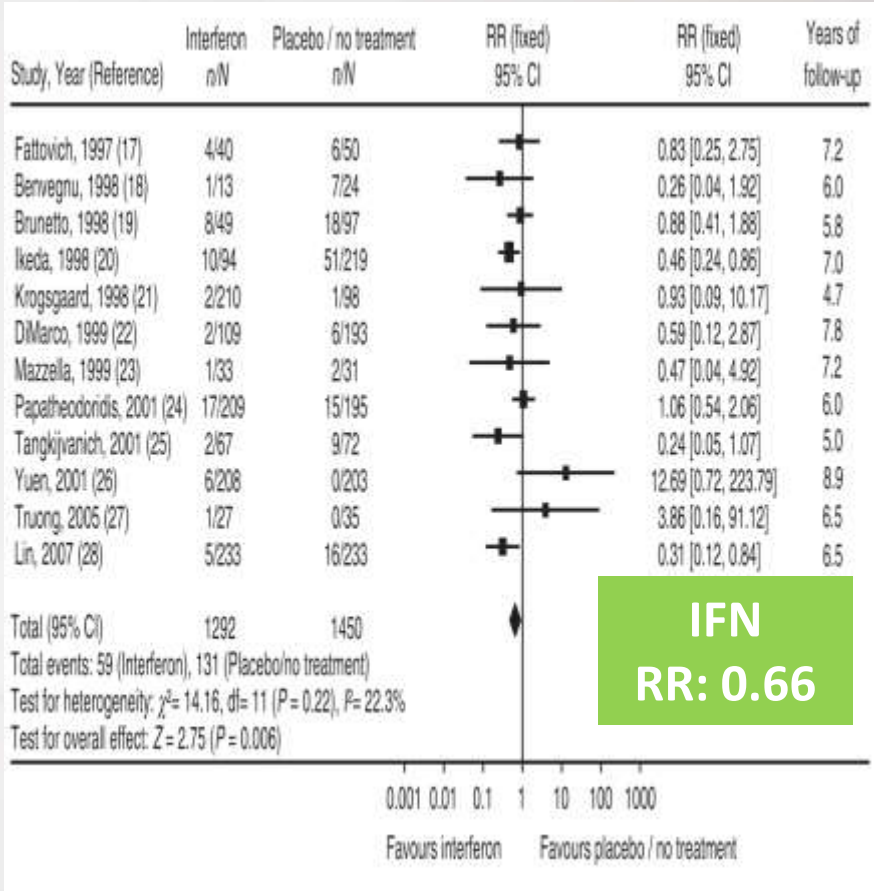
Liaw YF, Sung JJ et al. NEJM 2004

Antiviral therapy alters the natural history of chronic hepatitis B

Reduced risk of HCC





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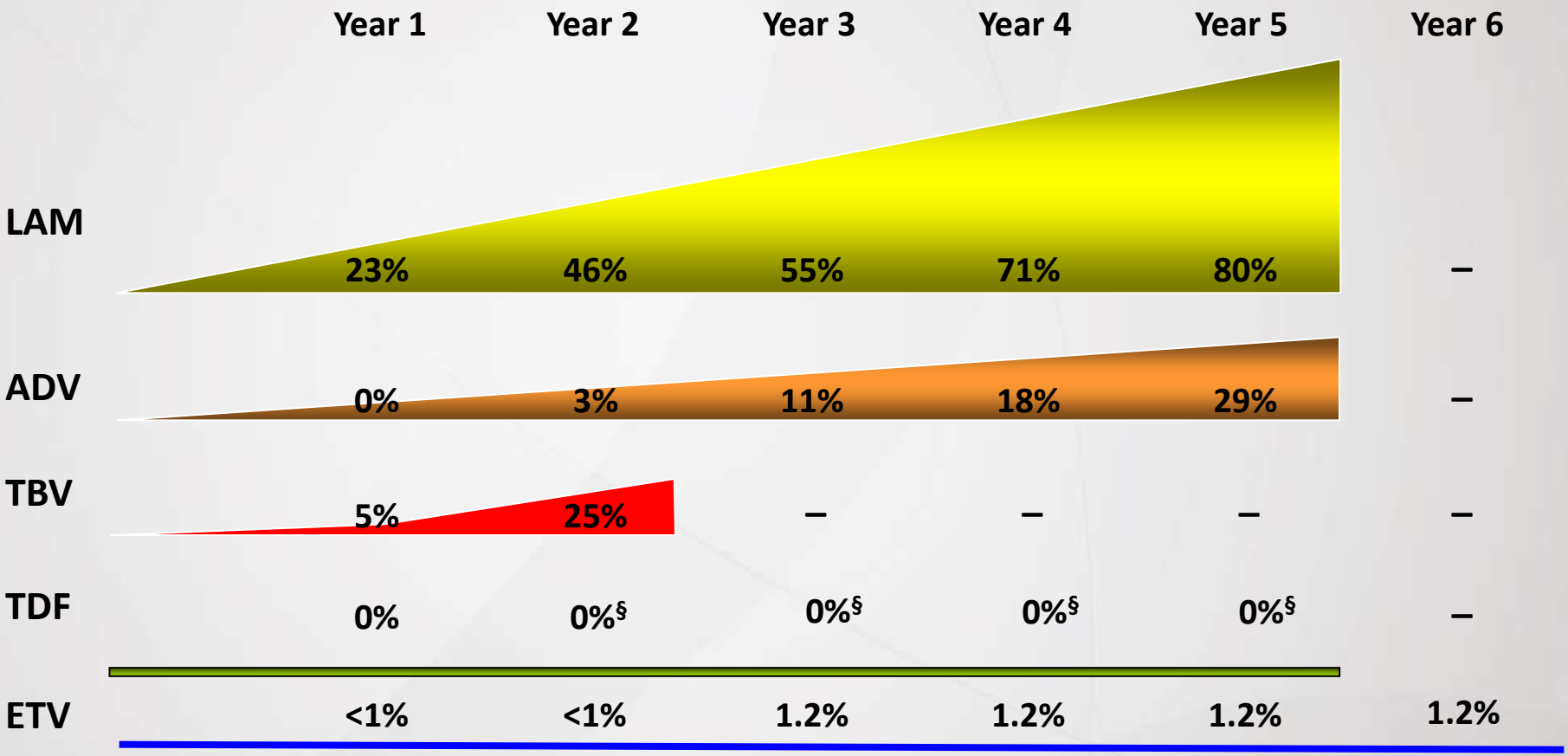
Sung JJY, et al. Aliment Pharmacol Ther 2008;28:1067-77

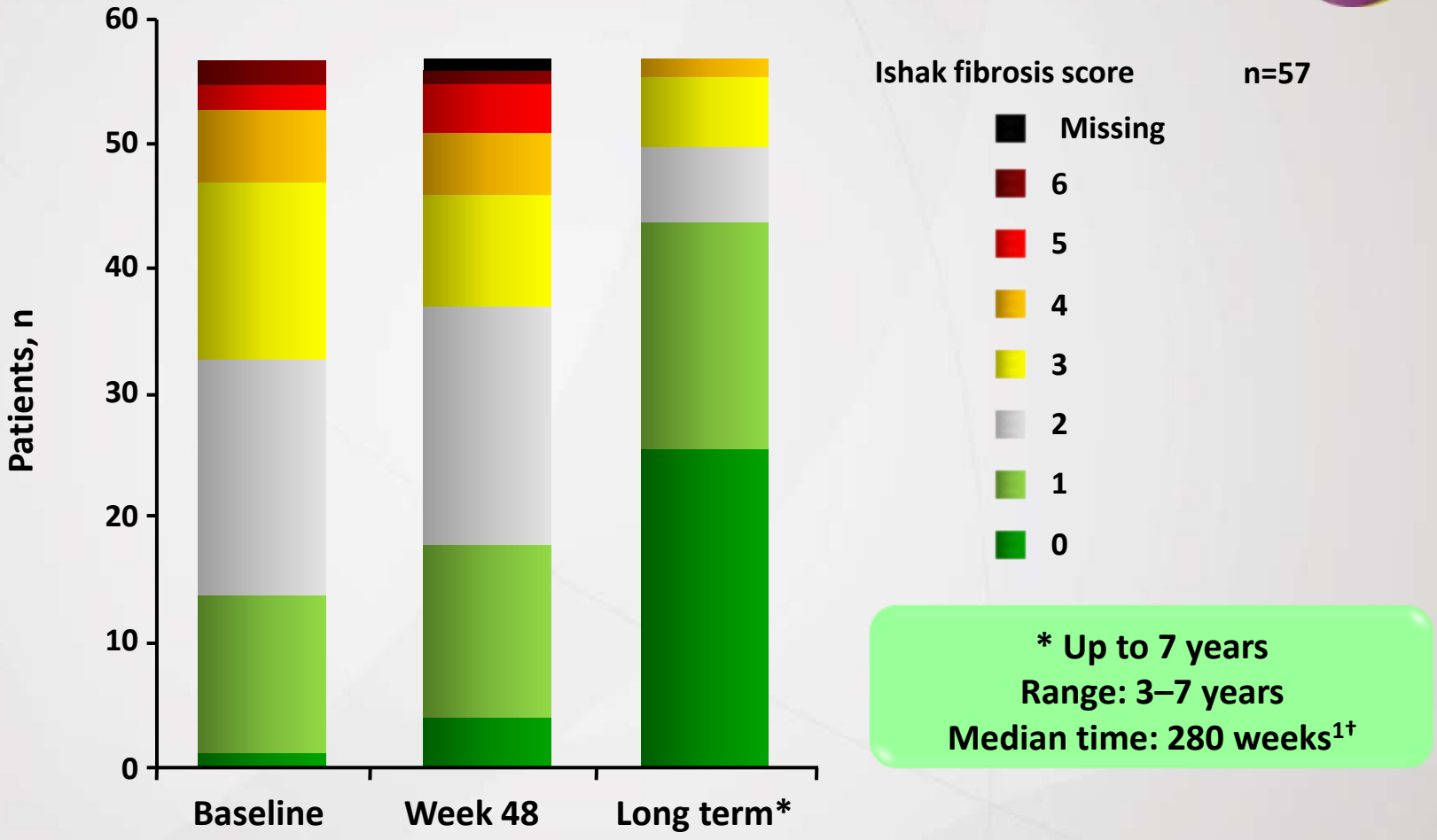
Would antiviral drug of lower drug resistance further reduce HCC?



§ Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF;
* Cumulative probabilities of resistance, ETV 1.0 mg dose used from year 3 onward

Antiviral therapy alters the natural history of chronic hepatitis B

Regression of liver fibrosis by entecavir



*** Up to 7 years**
Range: 3–7 years
Median time: 280 weeks[1†]

† In the randomized controlled studies, patients received 0.5 mg ETV. In the 901 rollover study, patients received 1 mg ETV.

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Chang TT, et al. Hepatology 2010

Antiviral therapy alters the natural history of chronic hepatitis B

Regression of liver fibrosis

Nucleos(t)ide analogues	n	HBeAg	Duration	Fibrosis Regression
Lamivudine	63	+	3 yrs	33%
Entecavir	21	+/-	3 yrs	57%
Adefovir	15/24	+/-	5 yrs	60%/71%
Entecavir	57	+/-	6 yrs	88%
Tenofovir	348 (96[b])	+/-	5 yrs	51% (74%[b])

Ishak score >1-point

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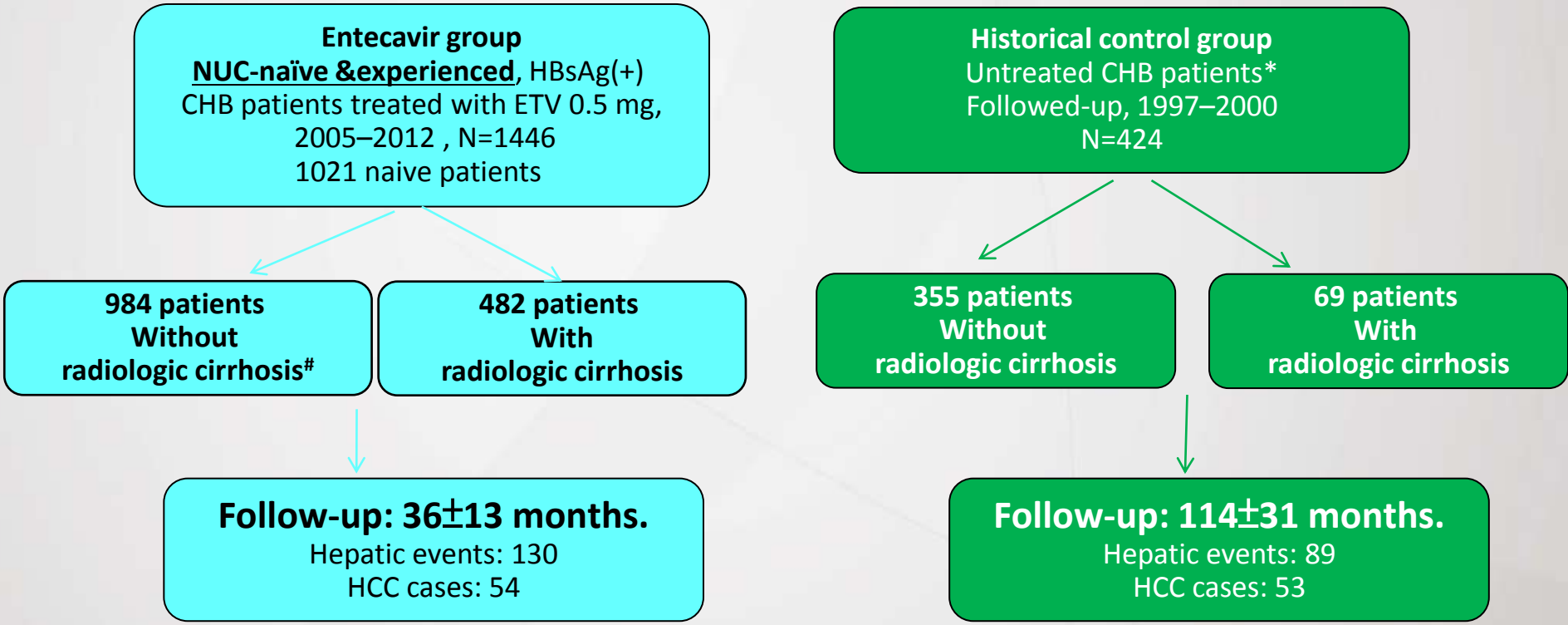
Adapted from Liaw YF Liver Int 2013

Hong Kong cohort study: ETV reduces hepatic events in cirrhotic patients

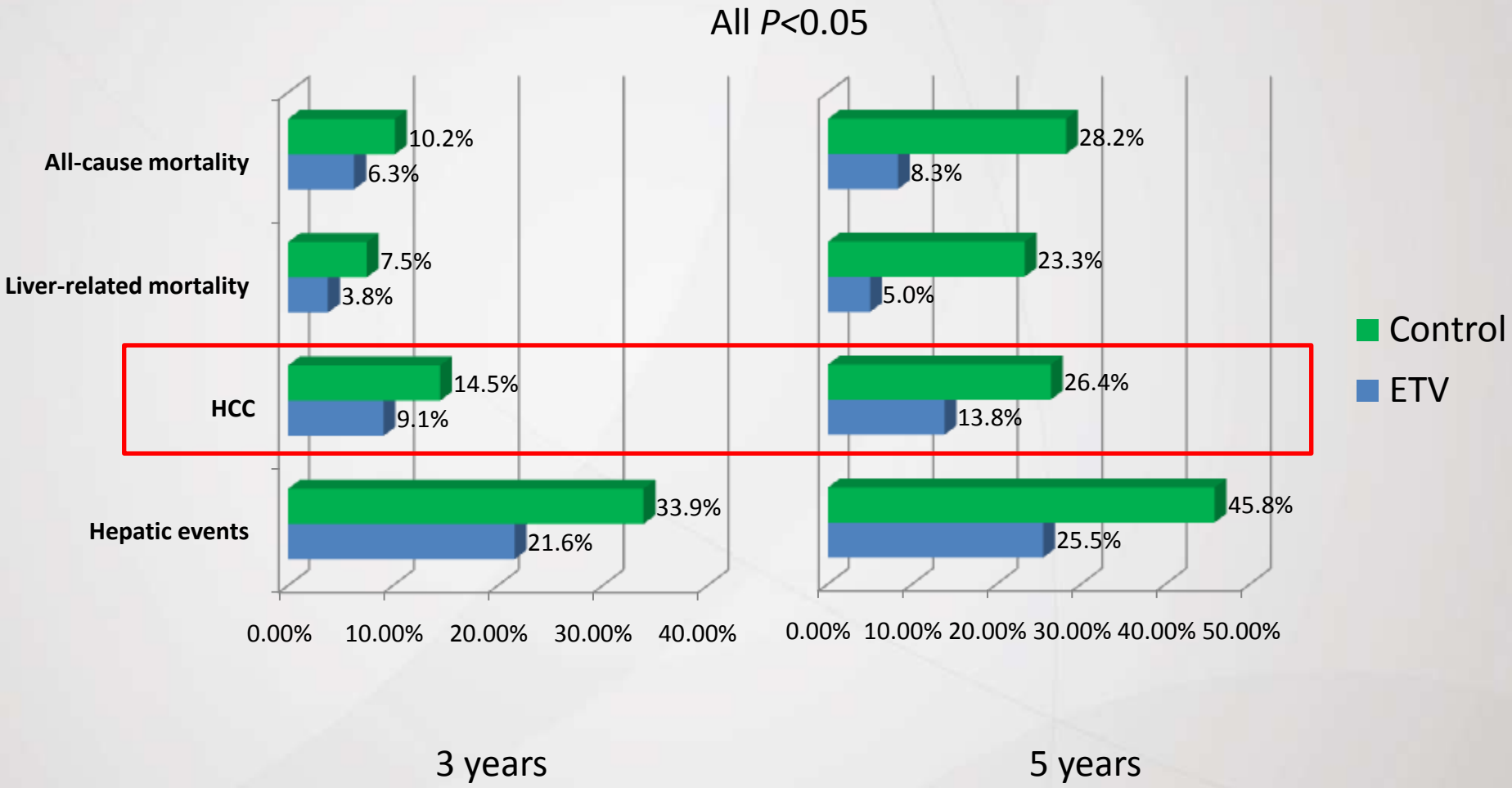
- Retro-prospective cohort study
- To compare clinical outcomes **(hepatic events: any cirrhotic complications, HCC and/or liver-related mortality)** with ETV vs. no treatment



Radiologic cirrhosis was defined as coarse liver echotexture with nodularity and small liver size or the presence of features of portal hypertension (*e.g., ascites, splenomegaly,* and varices) noted on liver imaging.

Wong GL, Chan HL, ……Wong VW. Hepatology 2013

Cumulative probabilities of hepatic events in cirrhotic patients



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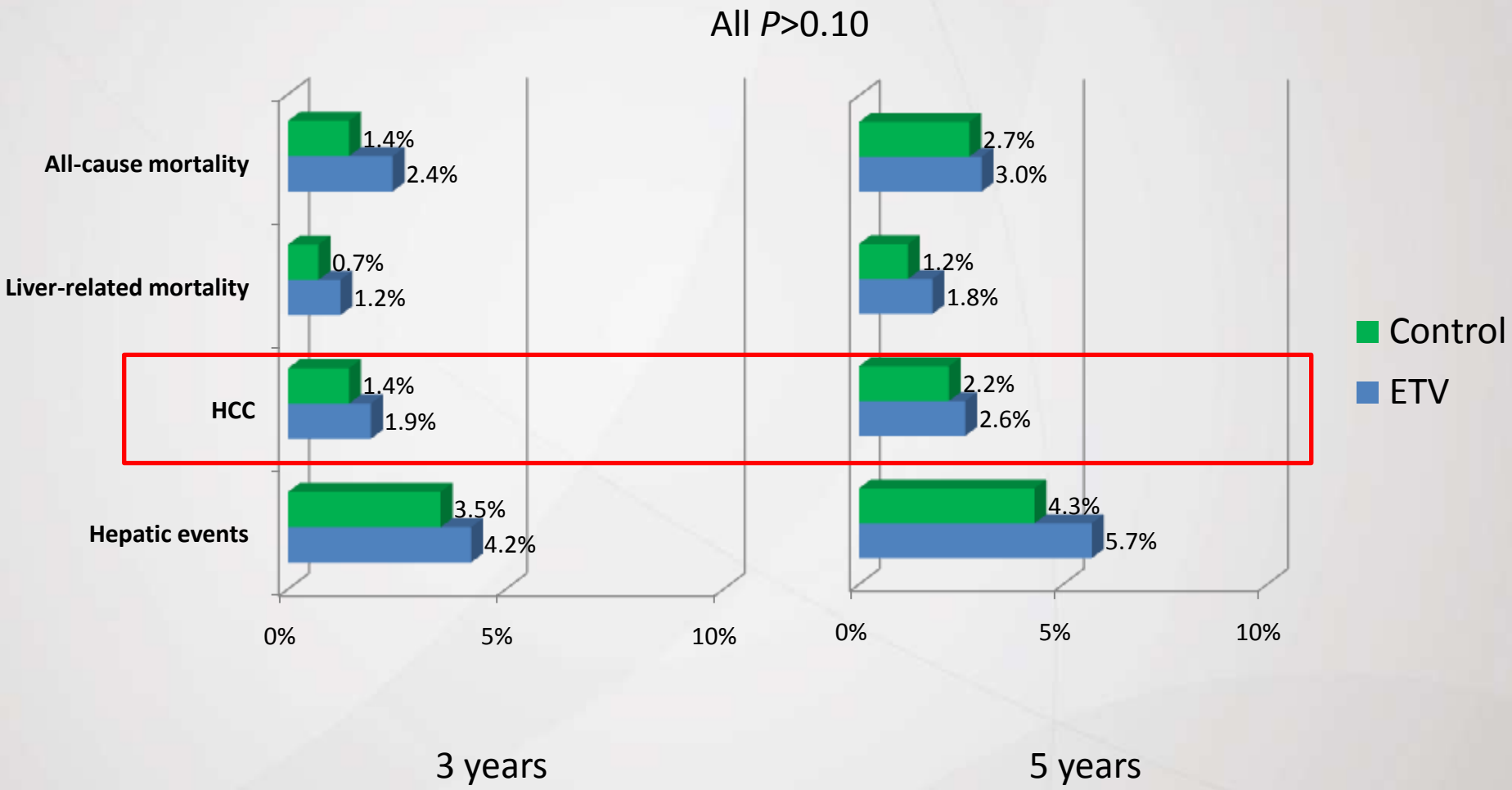
Wong GL, et al. Hepatology 2013

Cumulative probabilities of hepatic events (non-cirrhotic subgroup)



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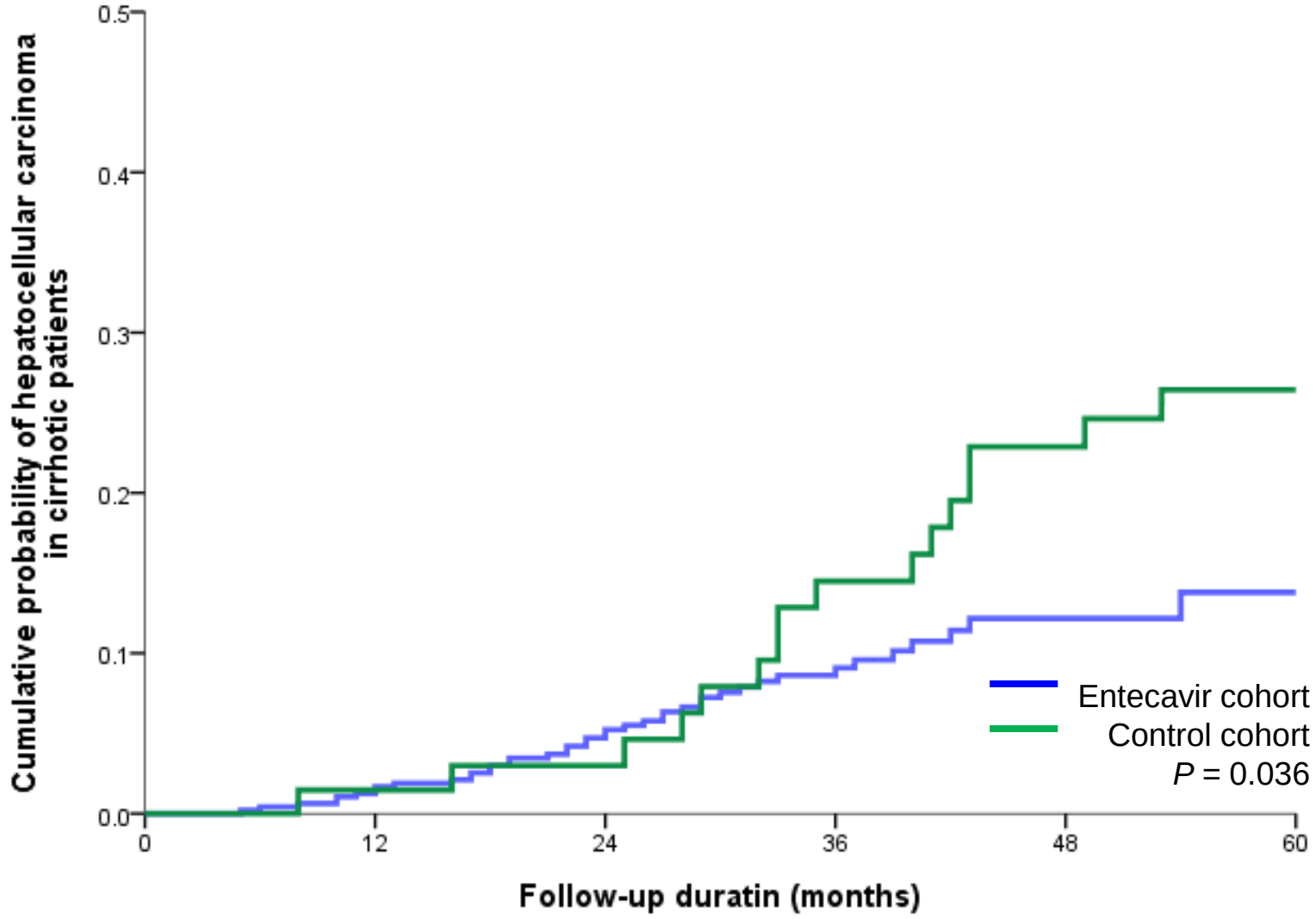
Entecavir therapy reduces HCC in cirrhotic patients



Patients at risk						
Entecavir cohort	482	466	365	194	81	20
Control cohort	69	65	60	52	45	41

Wong GL, et al. Hepatology 2013

Efficacy of entecavir therapy adjusted for MELD score and maintained viral suppression

Clinical outcomes	Hazard ratio	95% CI	P values
Hepatic events	0.51	0.34 – 0.78	0.002
HCC	0.55	0.31 – 0.99	0.049
Liver-related mortality	0.26	0.13 – 0.55	<0.001
All-cause mortality	0.34	0.18 – 0.62	<0.001

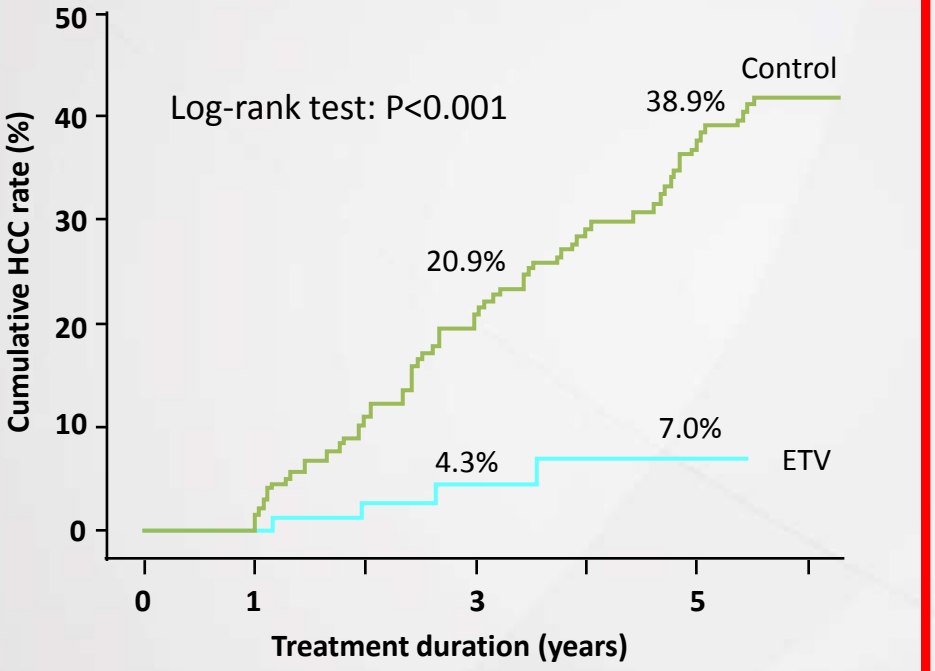
Sensitivity analyses on clinical parameters and 3-year probability of hepatic events

Patients with more advanced liver disease would benefit more from entecavir therapy

Clinical parameters	Hazard ratio*	95% CI	P values
Gender			
Male	0.5	0.4 – 0.8	0.001
Female	0.8	0.3 – 2.1	0.27
Platelet			
≤ 100 x10^9/l	0.4	0.3 – 0.7	<0.001
> 100 x10^9/l	1.1	0.6 – 1.7	0.33
Albumin			
≤ 35 g/l	0.6	0.5 – 1.1	0.07
> 35 g/l	1.1	0.6 – 1.9	0.33
Total bilirubin			
≤ 18 µmol/l	0.8	0.4 – 1.7	0.35
> 18 µmol/l	0.6	0.4 – 1.0	0.02
Baseline HBV DNA			
≤2000 IU/ml	1.3	0.5 – 5.1	0.91
>2000-200,000 IU/ml	0.7	0.4 – 1.4	0.11
>200,000 IU/ml	0.3	0.2 – 0.6	<0.001

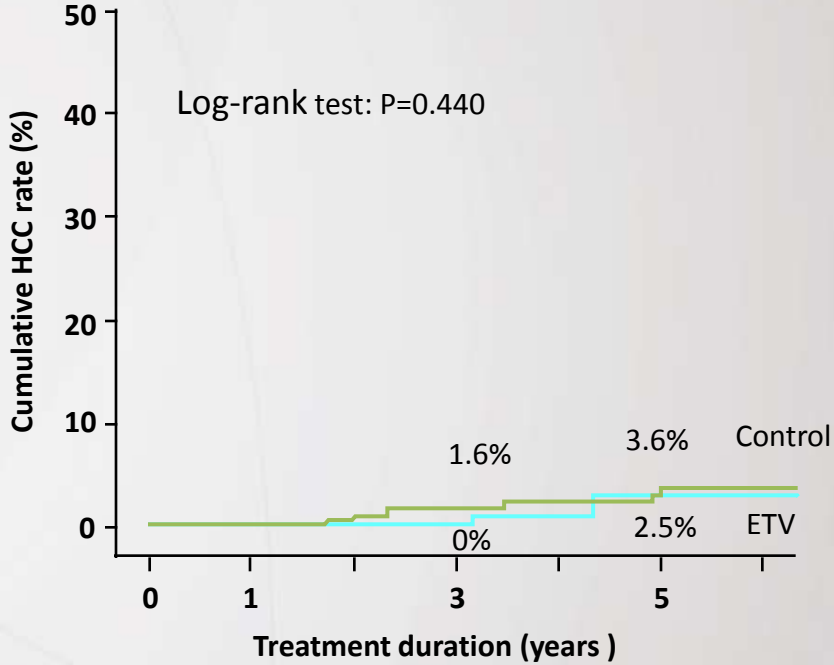
*Adjusted for MELD score and maintained viral suppression

Toranomon Hospital cohort: reduction in HCC incidence with ETV was greater among cirrhotic patients



No at risk

ETV	79	79	72	53	35	17
Control	85	85	76	65	54	47

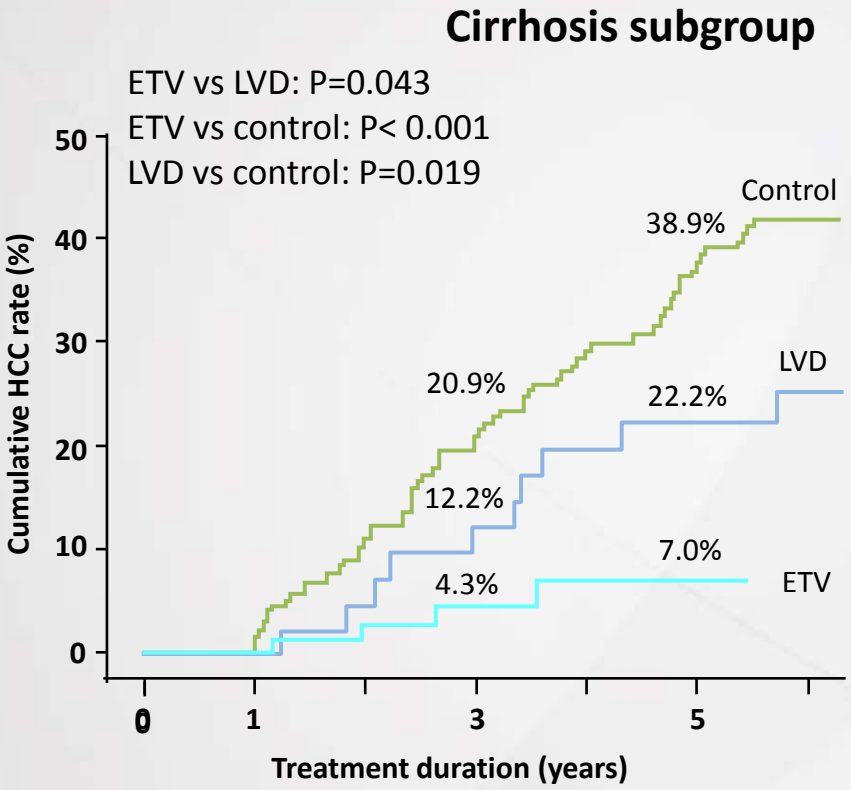


No at risk

ETV	237	237	192	132	66	27
Control	231	231	201	181	169	143

Hosaka T, et al. Hepatology, 2012

Toranomon Hospital cohort: HCC incidence was lower with ETV than with LVD



No at risk

ETV	79	79	72	53	35	17
Control	85	85	76	65	54	47
LVD	49	49	41	35	32	29

LVD cohort (N=182)

- Received no rescue therapy if LVD failure
- Effect is not significant in non-cirrhotic patients

Hosaka T, et al. Hepatology, 2012

Toranomon Hospital cohort: reduction in HCC with ETV was greatest among high-risk patients

Risk score	Risk (score)	n	Cumulative 5-year incidence of HCC (%)[1]		
			ETV	Control	P*
Yang HI 2011[2]	**Low (<12)**	1272	1.1	2.4	0.313
	High (≥12)	342	8.3	23.9	0.006
Yuen MF 2009[3]	**Low (<82)**	1110	0.7	0.5	0.914
	High (≥82)	505	7.2	21.0	0.002
Wong VWS 2010[4]	**Low (<4)**	1054	0.5	1.5	0.246
	Medium (4-19)	339	4.3	10.6	0.062
	High (≥20)	222	8.0	33.3	<0.001

Hosaka T, et al. Hepatology, 2012

Before HCC occurs……

WHO WILL DEVELOP HCC EVEN ON ANTIVIRAL?

Prediction scores for HBV-related HCC among treatment-naïve patients

Score	Patients	Components	rmance
CU-HCC	Clinic patients: 1005 in trainin in vali		V at 10
GA			10
REAC			% NPV at 10 years

Does the scores work in patients on antiviral therapy?

How to interpret changes in risk scores?

Wong VW et al. J Clin Oncol 2010;28:1660
Yuen MF et al. J Hepatol 2009;50:80
Yang HI et al. Lancet Oncol 2011;12:568

Factors associated with HCC

	Univariate analysis			Multivariate analysis		
Factors	HR	95% CI	P	aHR	95% CI	P
Male gender	1.4	0.7-2.5	0.46			
Age ≥50 years	48	0-5602	0.11			
Albumin <35 g/l	24	8-73	<0.001	14	4-43	<0.001
Bilirubin ≥18 µmol/l	4.1	1-21	0.10			
ALT >ULN	0.05	0-5×10^{13}	0.86			
Positive HBeAg	0.03	0-146	0.41			
Baseline HBV DNA ≥2000 IU/ml	1.7	0.7-4.0	0.24			
Baseline HBsAg ≥1000 IU/ml	0.6	0.3-1.2	0.14			
Cirrhosis	4.9	2.7-8.7	<0.001	3.2	1.5-6.4	0.002
Duration of virologic remission ≥24 months	0.4	0.2-0.7	0.01	0.3	0.1-0.6	0.007

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Wong GL, et al. Gastroenterology 2013

Area under time-dependent ROC curves of different HCC risk scores

	CU-HCC	GAG-HCC	REACH-B
Baseline	0.80	0.76	0.71
Year 1	0.77	0.77	0.74
Year 2	0.85	0.86	0.79
Year 3	0.95	0.95	0.97
Year 4	0.87	0.93	0.74

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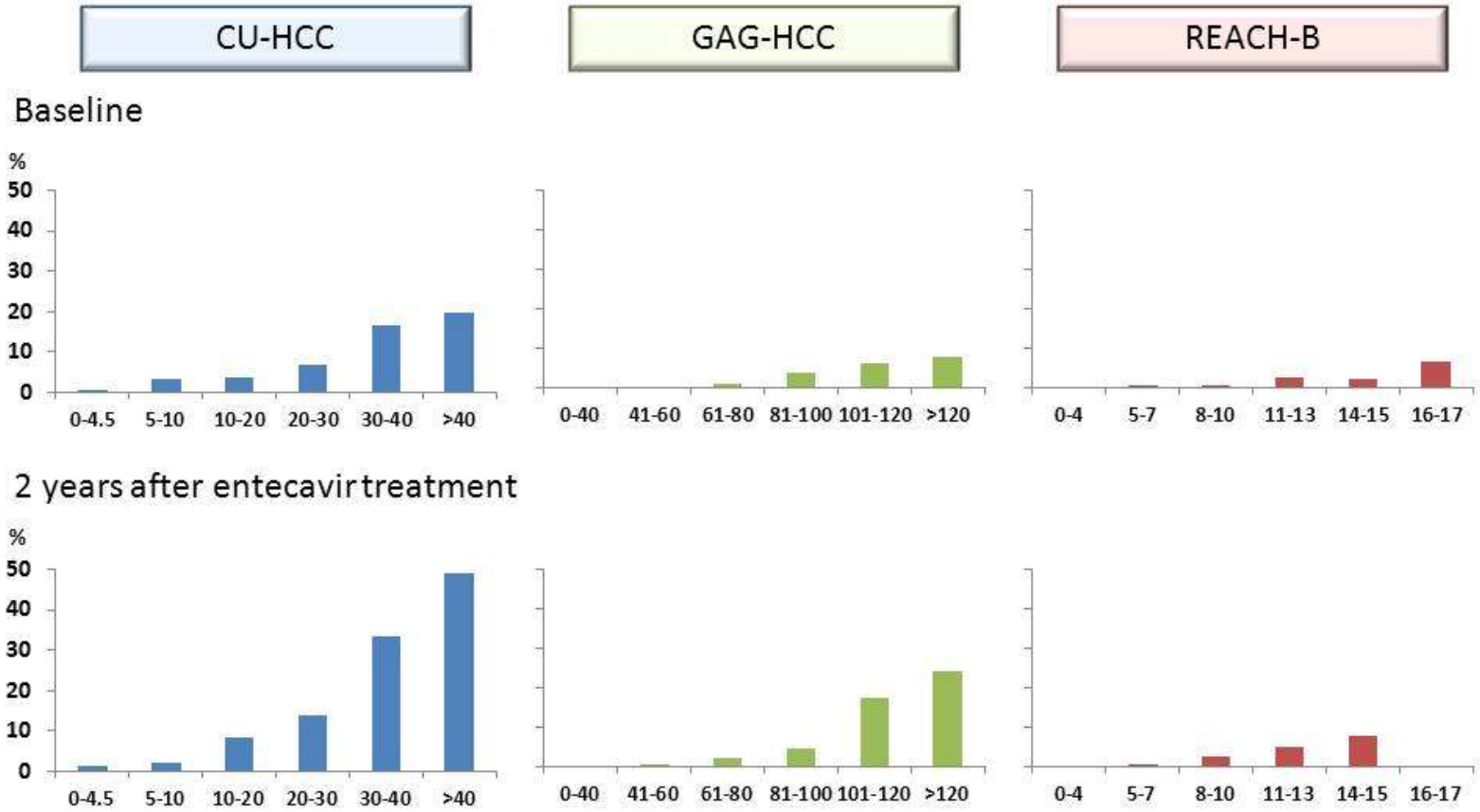
Risk of HCC in the next 3 years by risk scores



Wong GL, et al. Gastroenterology 2013

Performance of baseline and on-treatment HCC prediction scores

	CU-HCC	GAG-HCC	REACH-B
Baseline			
Sensitivity	94%	55%	95%
Specificity	48%	79%	17%
PPV	5%	8%	2%
NPV	100%	98%	100%
Year 2 on-treatment			
Sensitivity	86%	68%	100%
Specificity	56%	88%	53%
PPV	3%	8%	1%
NPV	100%	99%	100%

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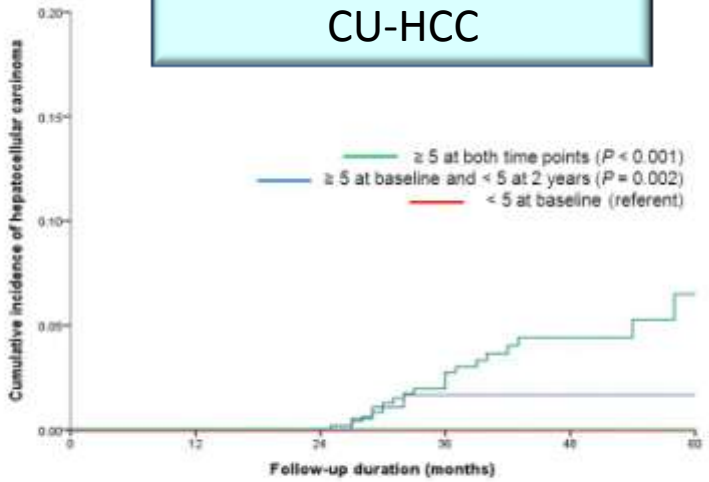
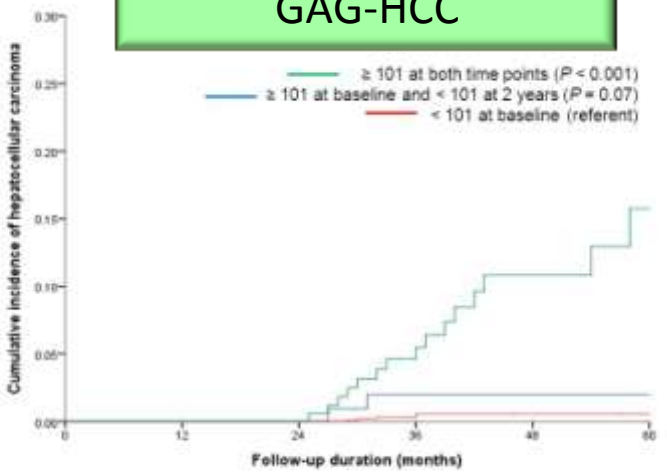
Reduction in risk scores leads to a lower risk of HCC

CU-HCC



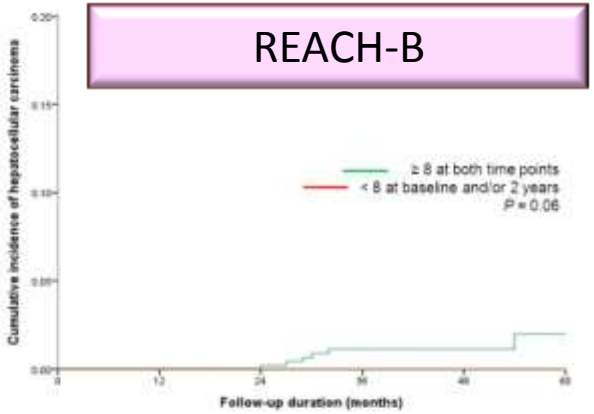
CU-HCC score at baseline and 2 years	Patients under observation					
≥ 6 at both	540	540	520	379	180	63
≥ 6 and < 6	197	197	187	147	78	43
< 6 at baseline	673	673	646	529	262	61

GAG-HCC



GAG-HCC score at baseline and 2 years	Patients under observation					
≥ 101 at both	187	187	183	113	58	26
≥ 101 and < 101	116	116	114	75	38	13
< 101 at baseline	1108	1108	1106	843	391	160

REACH-B



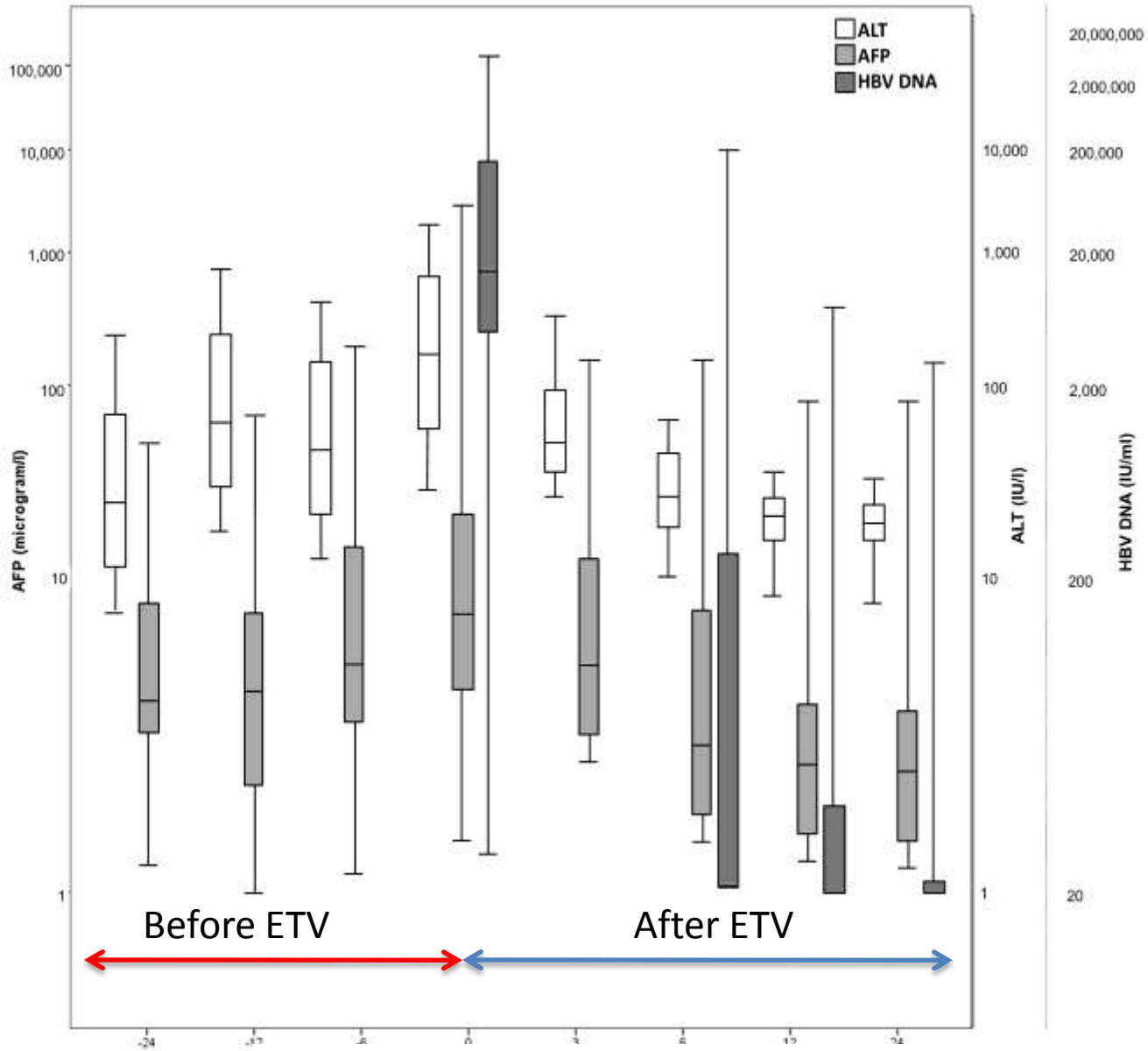
REACH-B score at baseline and 2 years	Patients under observation					
≥ 8 at both	499	499	495	371	176	64
< 8 at baseline or 2 years	616	616	609	412	231	116

Wong GL, et al. Gastroenterology 2013

Before HCC occurs……

WHAT IS THE EFFECT OF ANTIVIRAL ON TUMOR MARKER?

Entecavir reduces AFP elevation related to active hepatitis and inflammation



Wong GL, Chan HL, ……Wong VW. Hepatology 2013

On-treatment AFP is a more specific tumor marker for HCC in patients receiving entecavir

Author	Year of publication	Study type*	No. of subjects	No. of HCC	HBV# (%)	AFP cutoff (μg/l)	Sensitivity (%)	Specificity (%)
Treatment-naïve patients								
Di Bisceglie	1989	RC	166	2	100	25	100	88
Lok	1989	PC	290	6	100	20	100	87
Piantino	1989	CC	766	333	43.5	50	76	67
Lee	1991	CC	254	54	66.9	25	78	50
Oka	1994	PC	260	55	36.9	20	39	76
Sherman	1995	PC	1069	14	100	20	64	91
McMahon	2000	PC	1487	32	100	20	97	91
Trevisani	2001	CC	340	170	50.0	20	60	91
Tong	2001	PC	602	31	27.1	11	86	89
Marrero	2003	CC	207	55	12.1	20	77	71
Chen	2003	PC	5881	374	100	20	55	87
Marrero	2005	CC	352	144	32.4	112	25	97
Giannelli	2005	CC	251	120	15.0	12.6	45	87
Giannelli	2007	CC	961	499	12.1	18.8	41	94
Mao	2010	CC	4217	789	20.4	35	58	85
Shen	2012	CC	831, 453^	424, 209^	74.4, 75.1^	20	58, 67^	88, 64^
Wong	2013	PC	424	53	100	6	83	63
Patients receiving antiviral therapy								
Wong	**2013**	**PC**	**1531**	**57**	**100**	**6**	**81**	**80**
						20	**39**	**99**

Wong GL, Chan HL, ……Wong VW. Hepatology 2013

After HCC occurs……

DOES HIGH HBV DNA LEVEL INCREASE HCC RECURRENCE?

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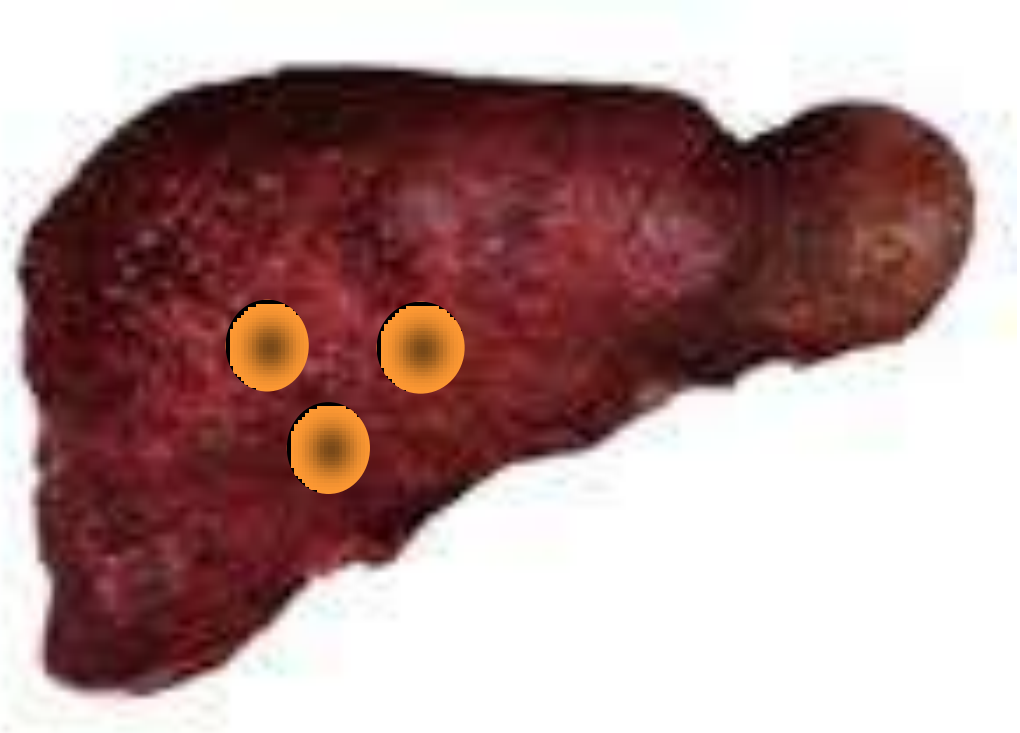
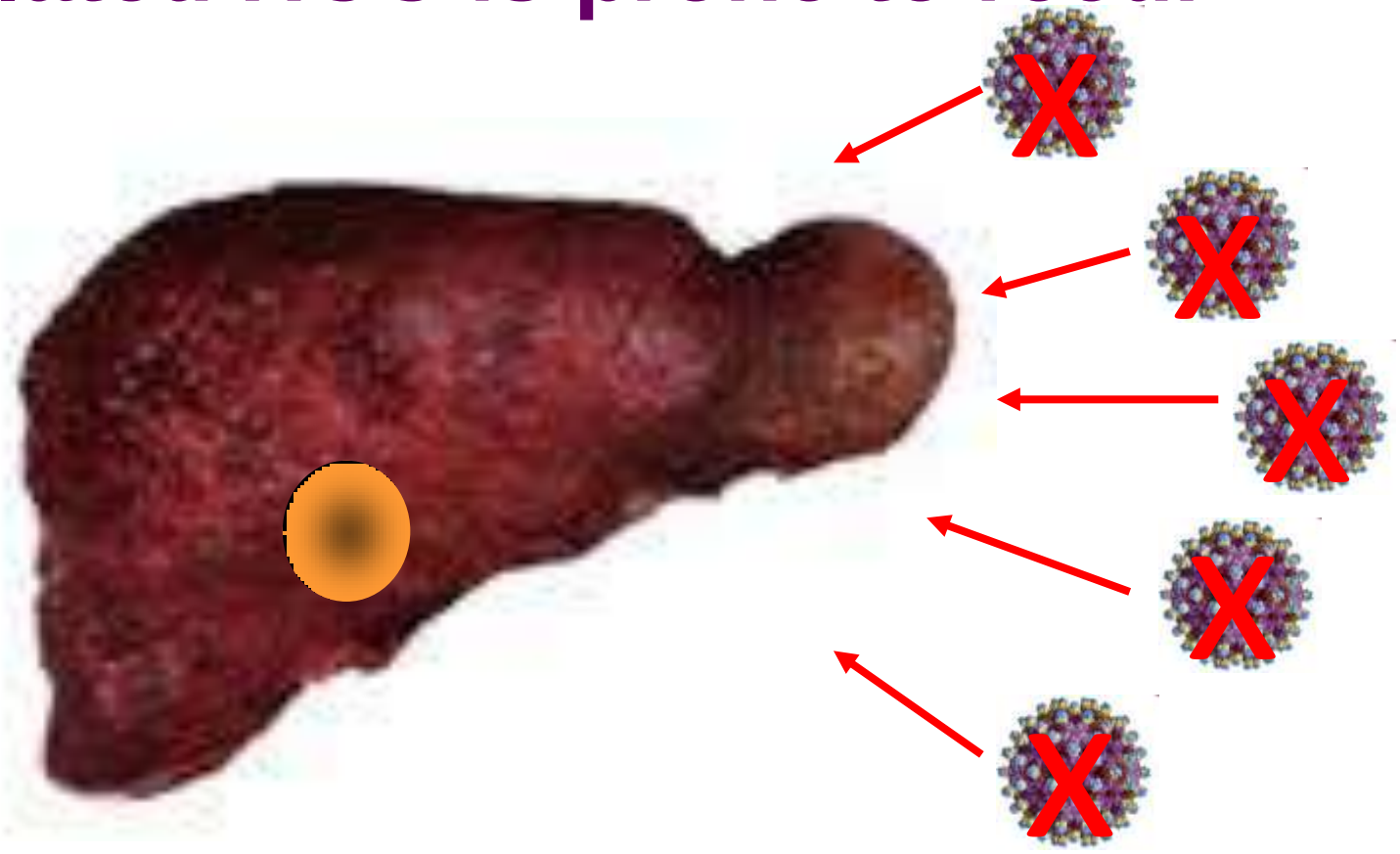
HBV-related HCC is prone to recur



HBV-related HCC is prone to recur



De novo recurrence

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ORIGINAL CONTRIBUTIONS

Liver

Recu
Carci
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Ivan F. N.
James Fu
[1]Departm
China

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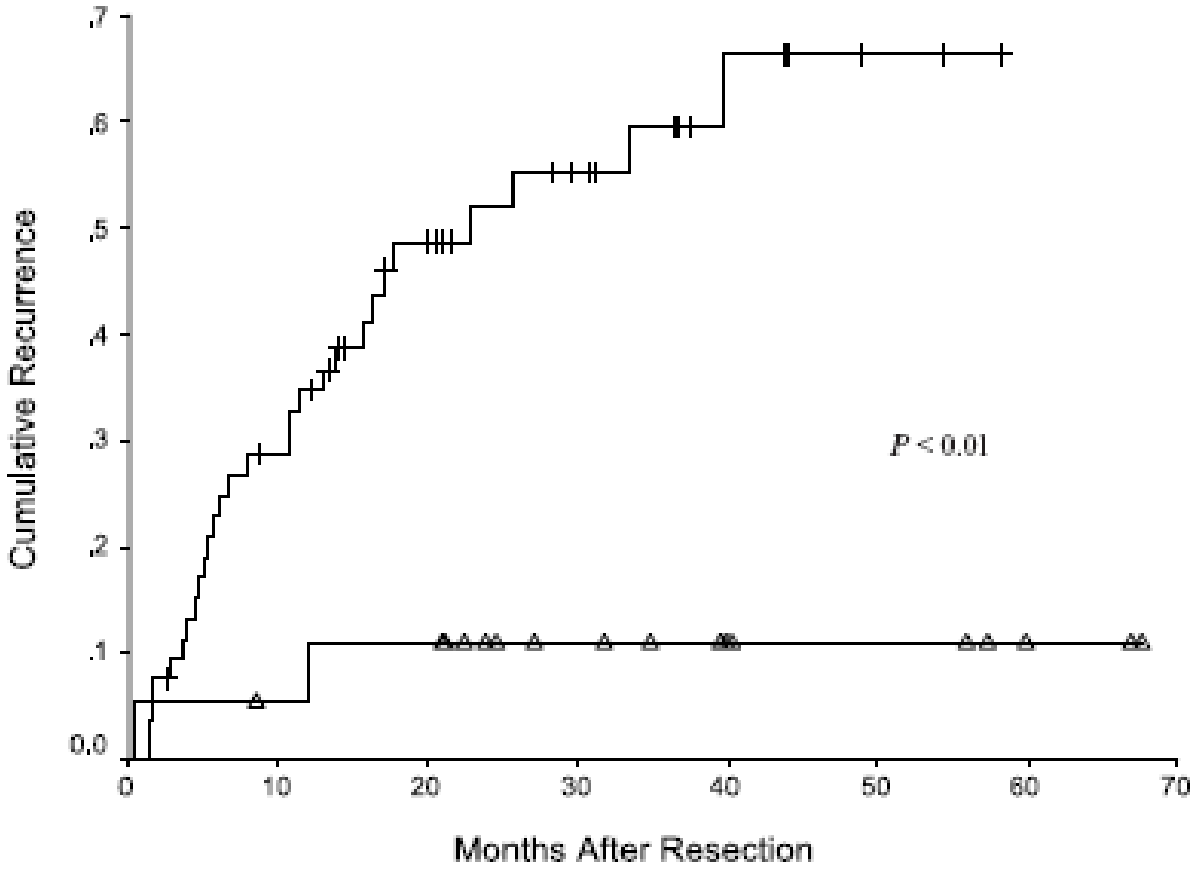

- 72
- In
  - + Initial viral load > 2000 IU/mL (4 $\log_{10}$ copies/mL)
  - Δ Initial viral load ≤ 2000 IU/mL (4 $\log_{10}$ copies/mL)
  - No post-operative antiviral therapy

Am J Gastroenterol 2008

ELSEVIER

Journal of Hepatology 51 (2009) 890–897

Journal of Hepatology

www.elsevier.com/locate/jhep

Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma☆

Jaw-Ching Wu[1,5,*,#], Yi-Hsiang Huang[2,5,#], Gar-Yang Chau[3,7,#], Chien-Wei Su[2,5,7], Chung-Ru Lai[4], Pui-Ching Lee[2], Teh-Ia Huo[2,6], I-Jane Sheen[5], Shou-Dong Lee[2,7], Wing-Yiu Lui[3,7]

- 193 patients, median FU 5 years
- Risk factors for early recurrence (<2 years)
  - Multinodularity, macroscopic venous invasion, resection margin ≤1cm
- Risk factors for late recurrence (>2 years)
  - Multinodularity, NI >6, ICG15 >10%, HBV DNA >10^6 copies/ml)

J Hepatol 2009

After HCC occurs……

DOES ANTIVIRAL THERAPY PREVENT HCC RECURRENCE?

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma

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SUMMARY

Background
The role of anti-viral therapy in prevention of hepatocellular carcinoma (HCC) recurrence is to be defined.

Aim
To investigate the role of anti-viral therapy in prevention of tumour recurrence after curative treatment of hepatitis B virus (HBV)-related HCC.

Methods
A systematic electronic search on keywords including HCC and different anti-viral therapies was performed through eight electronic databases, including Medline, EMBASE and Cochrane Databases. The primary outcome was HCC recurrence after curative treatment of HBV-related HCC.

Antiviral therapy reduces HCC recurrence

Study	Treated with antiviral Events	Total	Untreated Events	Total	Weight	OR, 95% CI
Chuma 2009	8	20	22	64	16.7%	1.27 [0.45, 3.57]
Hung 2008	0	10	30	62	3.0%	0.05 [0.00, 0.90]
Koda 2009	17	22	12	14	7.0%	0.57 [0.09, 3.42]
Kubo 2007	2	14	5	10	6.1%	0.17 [0.02, 1.16]
Kuzuya 2007	7	16	15	33	13.4%	0.93 [0.28, 3.11]
Li 2010	33	43	33	36	10.9%	0.30 [0.08, 1.19]
Piao 2005	14	30	26	40	18.3%	0.47 [0.18, 1.24]
Shuqun 2006	14	16	17	17	2.5%	0.17 [0.01, 3.73]
Yoshida 2008	18	33	40	71	22.1%	0.93 [0.41, 2.13]
Total (95% CI)		204		347	100.0%	0.59 [0.35, 0.97]
Total events	113		200			

Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 10.19$, df = 8 ($P = 0.25$); $I^2 = 21\%$

Test for overall effect: $Z = 2.06$ ($P = 0.04$)

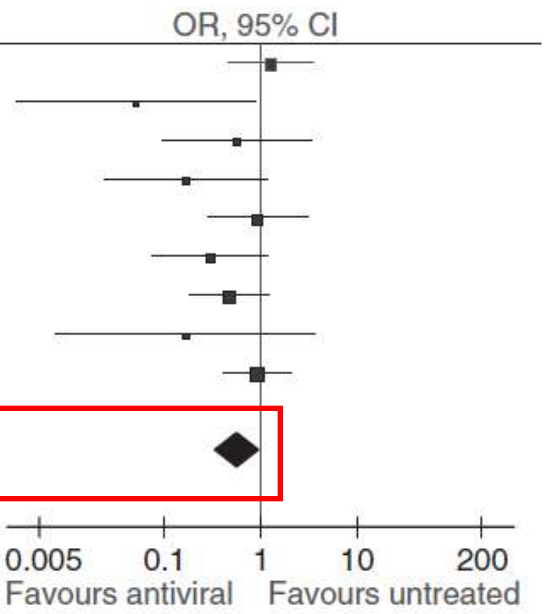

Figure 2 | The Forest plot to compare the effect of anti-viral treatment vs. no treatment in hepatocellular carcinoma recurrence.

Wong et al. Aliment Pharmacol Ther 2011

Study	Treated with antiviral Events	Total	Untreated Events	Total	Weight	OR, 95%CI
Hung 2008	0	10	0	62		Not estimable
Kubo 2007	0	14	0	10		Not estimable
Kuzuya 2007	0	16	3	33	31.4%	0.26 [0.01, 5.43]
Piao 2005	0	30	8	40	34.3%	0.06 [0.00, 1.13]
Yoshida 2008	0	33	7	71	34.3%	0.13 [0.01, 2.32]
Total (95% CI)		103		216	100.0%	0.13 [0.02, 0.69]
Total events	0		18			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.46$, df = 2 ($P = 0.79$); $I^2 = 0\%$
Test for overall effect: $Z = 2.40$ ($P = 0.02$)

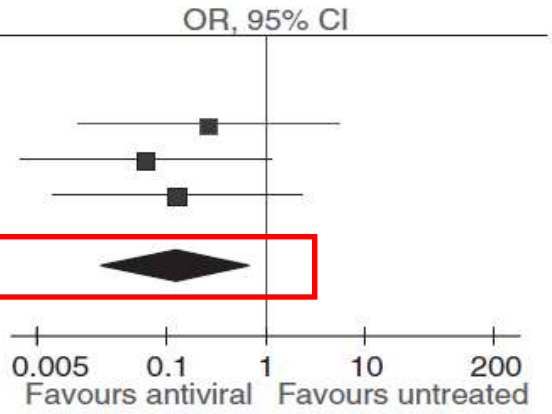

Figure 5 | The Forest plot to compare the effect of anti-viral treatment vs. no treatment in mortality secondary to liver failure.

Study	Treated with antiviral Events	Total	Untreated Events	Total	Weight	OR, 95%CI
Hung 2008	0	10	7	62	4.5%	0.35 [0.02, 6.65]
Koda 2009	4	22	7	14	17.3%	0.22 [0.05, 1.00]
Kubo 2007	0	14	3	10	4.1%	0.07 [0.00, 1.63]
Kuzuya 2007	0	16	6	33	4.5%	0.13 [0.01, 2.43]
Li 2010	41	43	36	36	4.2%	0.23 [0.01, 4.89]
Piao 2005	2	30	12	40	15.6%	0.17 [0.03, 0.81]
Shuqun 2006	15	16	17	17	3.7%	0.30 [0.01, 7.79]
Yoshida 2008	8	33	32	71	46.1%	0.39 [0.15, 0.98]
Total (95% CI)		184		283	100.0%	0.27 [0.14, 0.50]
Total events	70		120			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.01$, df = 7 ($P = 0.96$); $I^2 = 0\%$
Test for overall effect: $Z = 4.15$ ($P < 0.0001$)

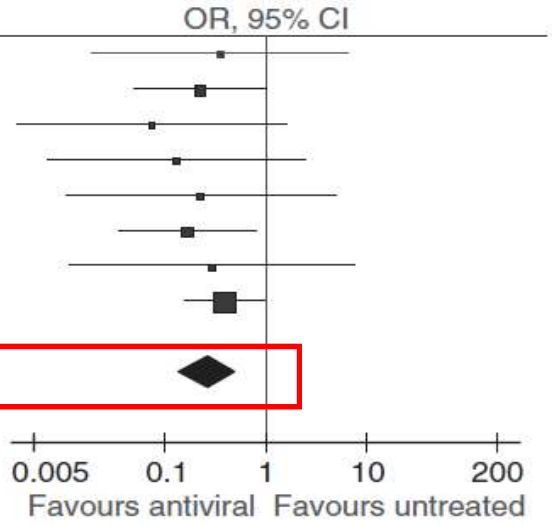

Figure 6 | The Forest plot to compare the effect of anti-viral treatment vs. no treatment in overall mortality.

The meta-analysis has provided strong evidence to support the use of antiviral drugs to prevent HCC recurrence

Patients before and/or after curative or local–regional therapy of HCC

Since most HCCs develop in patients with cirrhosis or advanced fibrosis, their underlying liver diseases should be managed or treated as in their counterparts without HCC.

Recommendation 17 Nuc treatment should be commenced in all HCC patients with HBV DNA >2,000 IU/mL before and/or after curative therapy of HCC as in their counterparts without HCC (IIIB). Preemptive nuc therapy should be initiated in all HCC patients who are to undergo transarterial chemoembolization (IIA).

Liaw, YF, Kao JH, Piratvisuth T, Chan HL, et al. APASL consensus statement on the management of chronic hepatitis B 2012

ONLINE FIRST

Association Between Nucleoside Analogues and Risk of Hepatitis B Virus–Related Hepatocellular Carcinoma Recurrence Following Liver Resection

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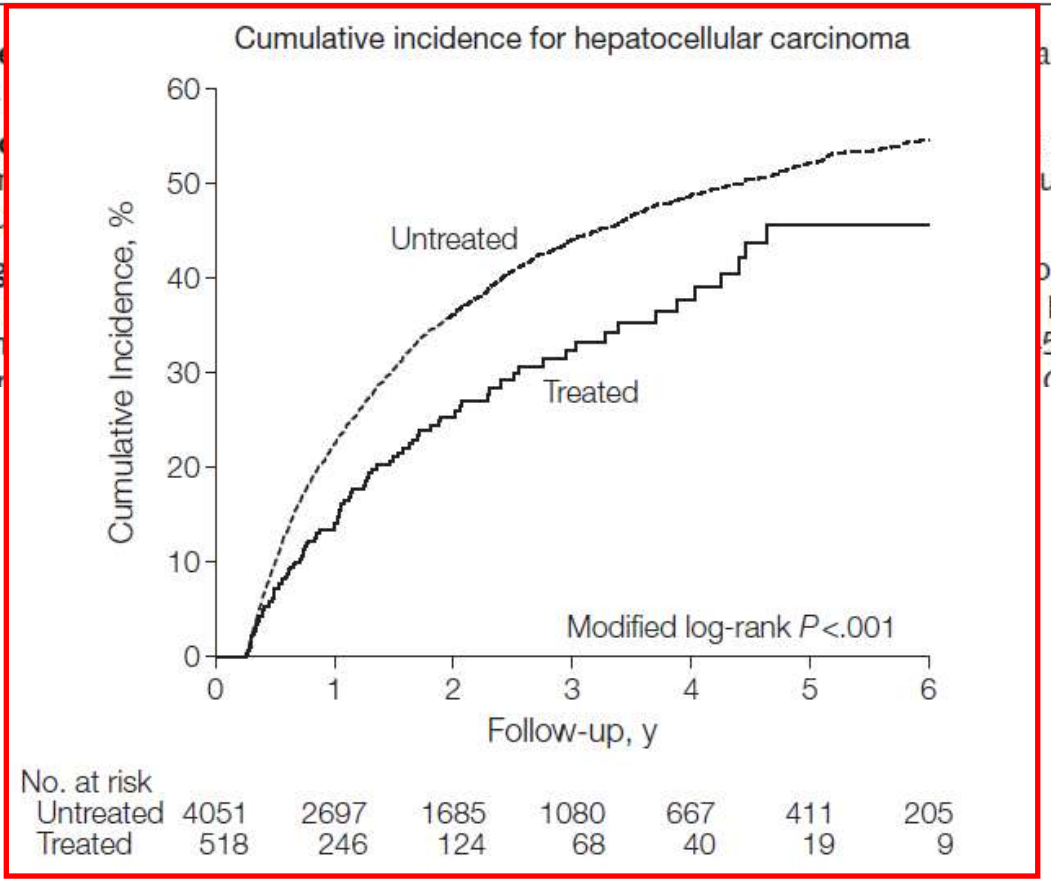
100 938 Patients admitted for the first time with primary diagnosis of HCC and registered in the Registry for Catastrophic Illness Patient Database

↓

4569 Included in the study cohort
- 4051 HBV patients did not receive antiviral therapy (untreated cohort)
- 518 HBV patients received antiviral therapy (treated cohort)



Wu CY, et al. JAMA 2012

Conclusions

- Entecavir reduces HCC occurrence.
- HCC risk scores remains accurate in entecavir-treated patients.
- AFP is a more specific tumor maker in entecavir-treated patients.
- High HBV DNA level is associated with HCC recurrence (esp. *de novo* recurrence).
- Antiviral therapy improves outcomes of HCC by improving liver function and reducing HCC recurrence.