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Impact of HBV therapy on the incidence of hepatocellular carcinoma

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Speaking and teaching: Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex, Merck, Janssen

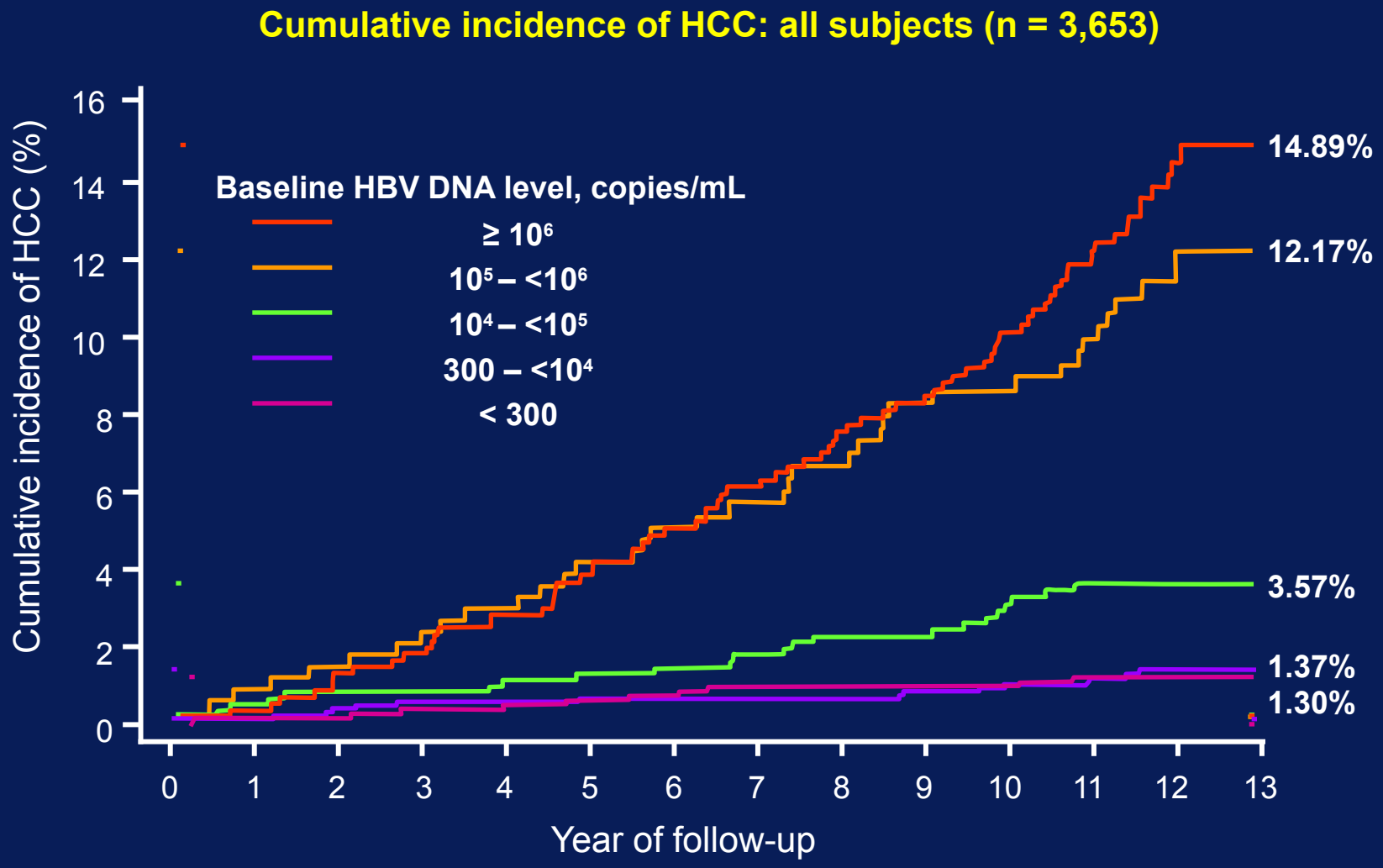
Primary Prevention Strategies of Hepatocellular Carcinoma (HCC)

1. Avoiding exposure to environmental risk factors

2. Chemoprevention

- *Cause specific agents* — *universal HB vaccination*; *anti-HBV/HCV therapy*
- *Cancer modifying agents* — *statins, metformin, TZD, coffee, aspirin*

High HBV Viral Load is Associated with Increased Incidence of HCC: The REVEAL Study



Chen et al. JAMA 2006;295:65-73.

Why Studies of Hepatitis B Therapy May Fail to Assess HCC Chemoprevention by IFN

1. Designed to assess antiviral efficacy of IFN by surrogate end-points.

   ➡ *Underpowered to capture hard end-points of hepatitis including HCC*

2. Enrolment skewed towards less severe hepatitis to improve compliance.

   ➡ *Risk of HCC diluted*

3. Different length/accuracy of f-up between responders and non responders.

   ➡ *Selection bias*

4. Lack of pretreatment patient stratif cation by HCC predictors

   ➡ *Comparison between studies compromised*

Meta-analyses on HBV-related HCC Chemoprevention by IFN Regimens

Authors	No. Studies	No. treated vs controls	Relative risk/risk difference* (95% CI)	P value
Sung et al 2008[3]	12	1,292 vs 1,458	0.66 (0.48 – 0.89)	0.006
Yang et al 2009[4]	11	1,006 vs 1,076	0.59 (0.43 – 0.81)	0.001
Miyake et al 2009[2]	8	553 vs 750	5.0%* (9.40 – 0.50)	0.028
Camma et al 2001[1]	**7**	853 vs 652	4.8%* (0.11 – 0.02)	NS
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Jin et al 2011[6]	9	1,291 vs 1,048	0.274 (0.06 – 1.03)	NS

1. Camma et al. J Hepatol 2001;34:593-602. 2. Miyake Y et al. J Gastroenterol 2009;44:470-5. 3. Sung JJ, et al. Aliment Pharmacol Ther 2008;28:1067-77. 4. Yang YF et al. J Viral Hepat 2009;16:265-71. 5. Zhang CH et al. Int J Cancer 2011;129:1254-64. 6. Jin H et al. Hepatol Res 2011;41:512-23.

The Clinical Benefits in Sustained Responders to IFN Regimens

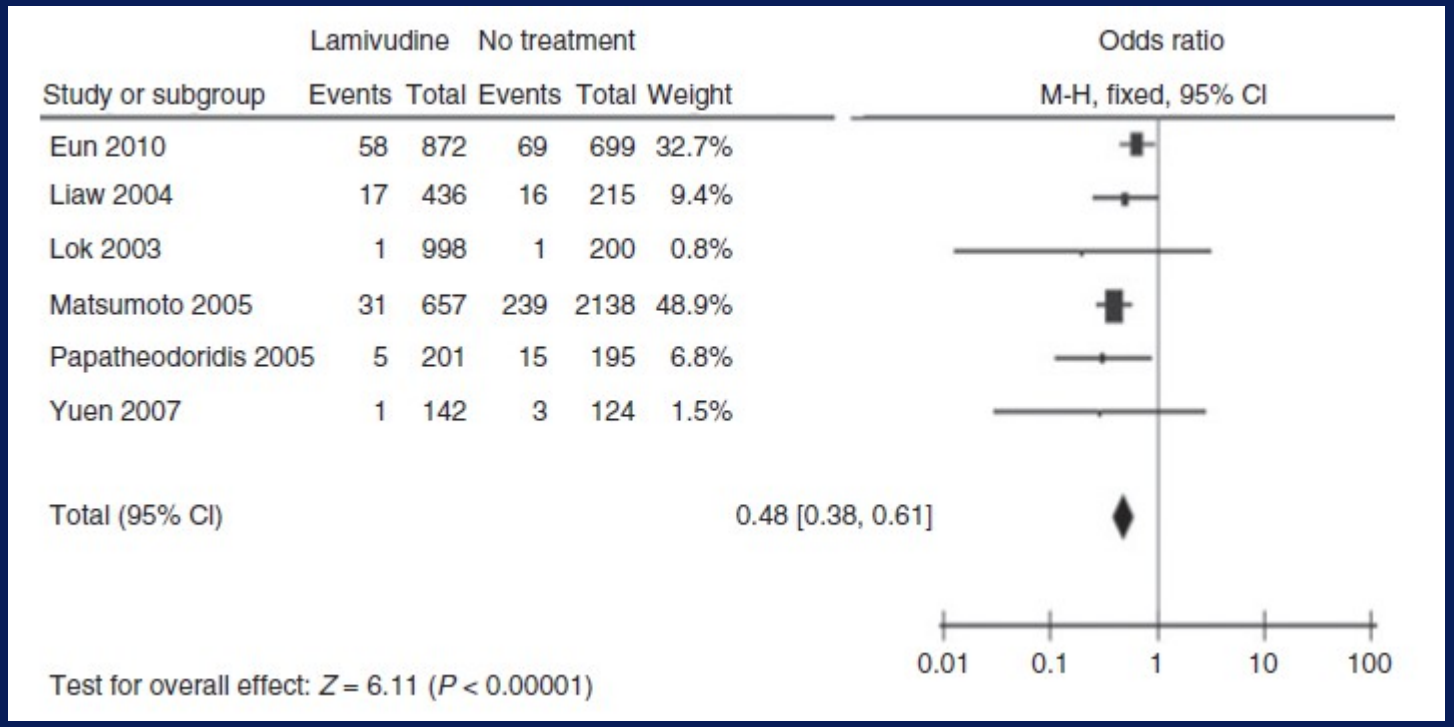
HBeAg (+)	Higher rates of *e-antigen* seroconversion and HBsAg clearance
	Prevention/reversal of cirrhosis, prevention of decompensation
	Risk reduction of HCC in cirrhotics only?
HBeAg (-)	High rates (up to 50%) of off-treatment HBsAg clearance
	Prevention/reversal of cirrhosis, prevention of decompensation
	Risk reduction of HCC in cirrhotics only?

Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease

Outcome	Lamivudine (n=436)	Placebo (n=215)	Hazard Ratio (95% CI)	p-value
Overall disease progression	34 (7.8%)	38 (17.7%)	0.45 (0.28 – 0.73)	0.001
Increase in Child-Pugh score	15 (3.4%)	19 (8.8%)	0.45 (0.22 – 0.90)	0.02
Hepatocellular carcinoma	17 (3.9%)	16 (7.4%)	0.49 (0.25 – 0.99)	0.047
Renal insufficiency	2 (0.5%)	0	–	–
Bleeding varices	2 (0.5%)	3 (1.4%)	–	–
Spontaneous bacterial peritonitis	0	0	–	–
Liver-related death	0	0	–	–

Liaw YF, et al NEJM 2004;351:1521-1531

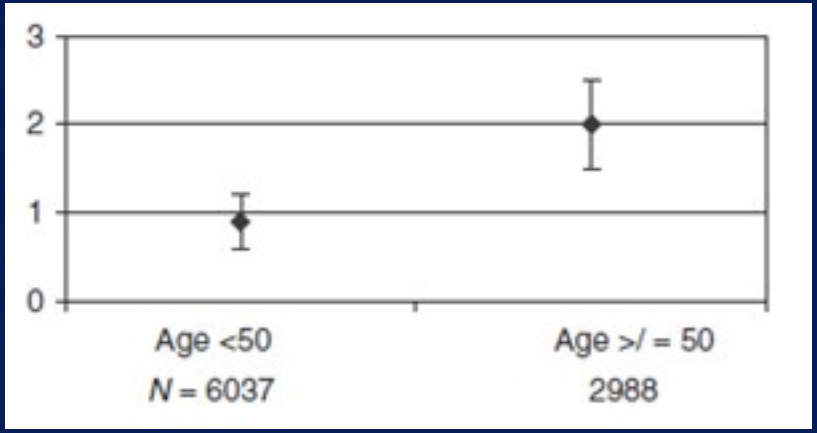
Meta-analysis: The Impact of Oral Anti-viral Agents on the Incidence of HCC in Chronic Hepatitis B



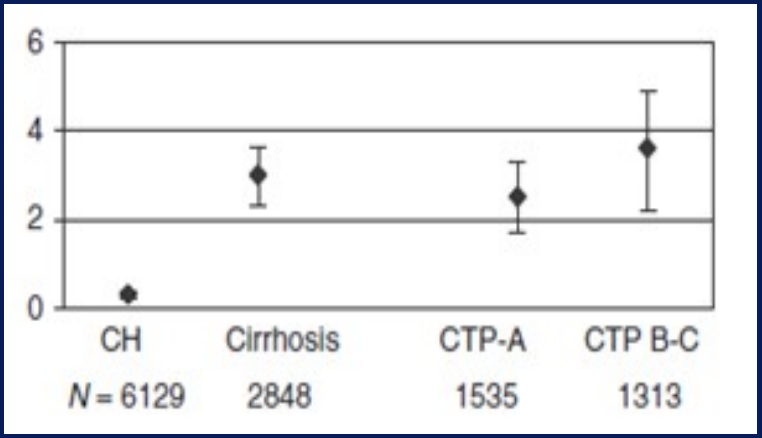
Singal et al, AP&T 2013;38:99-106

Meta-analysis of NUC Therapy: Pooled Data On the HCC Rate Per 100 HBV Patient Years Follow-up

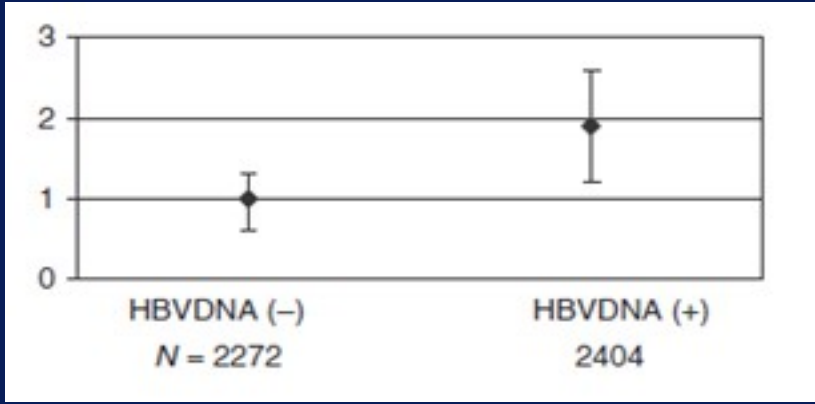
HCC rate: 0.9 vs 2.0*



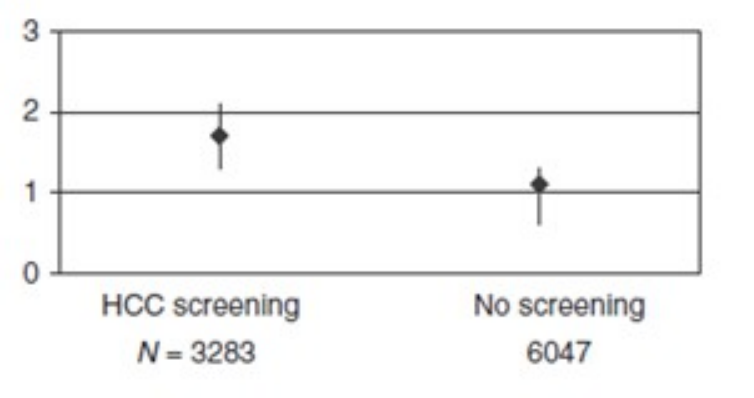
HCC rate: 0.3 vs 3.0*



HCC rate : 1.0 vs 1.9*



HCC rate : 1.7 vs 1.1*



Singal et al, AP&T 2013;38:99-106

*statistically signif cant differences

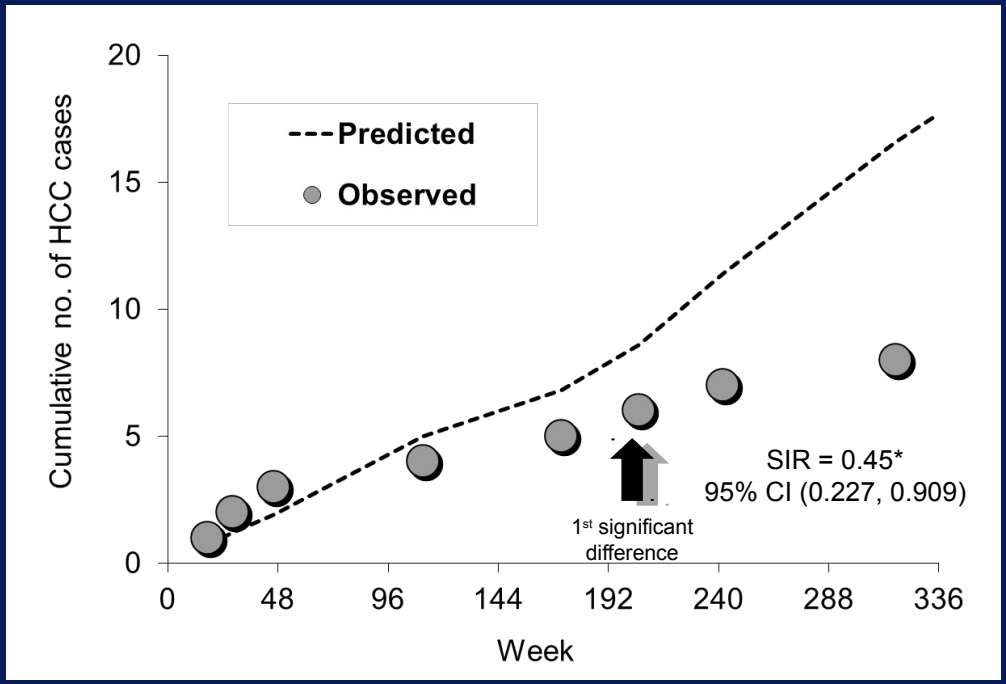
Development of HCC in HBV Patients Under Continuous NUCs Therapy

Study	F-up (mo.)	HCC in F0-3	HCC in F4
ETV Hong Kong[1]	42 +/- 13	18/813 (0.8% x yr)	21/247 (2.7% x yr)
ETV Japan[2]	38	2/237 (0.5% x yr)	4/79 (1.4% x yr)
ETV Italy[3]	60	6/209 (0.3% x yr)	18/155 (2.6% x yr)
TDF EU [4]	48	6/244 (1.0% x yr)	10/99 (4.2% x yr)
TDF EU [5]	17 (2-58)	19/780 (0.5% x yr)	33/402 (4.1% x yr)
Untreated[6]	Asia	0.6% x yr	3.7% x yr
	Europe	0.3% x yr	2.2% x yr

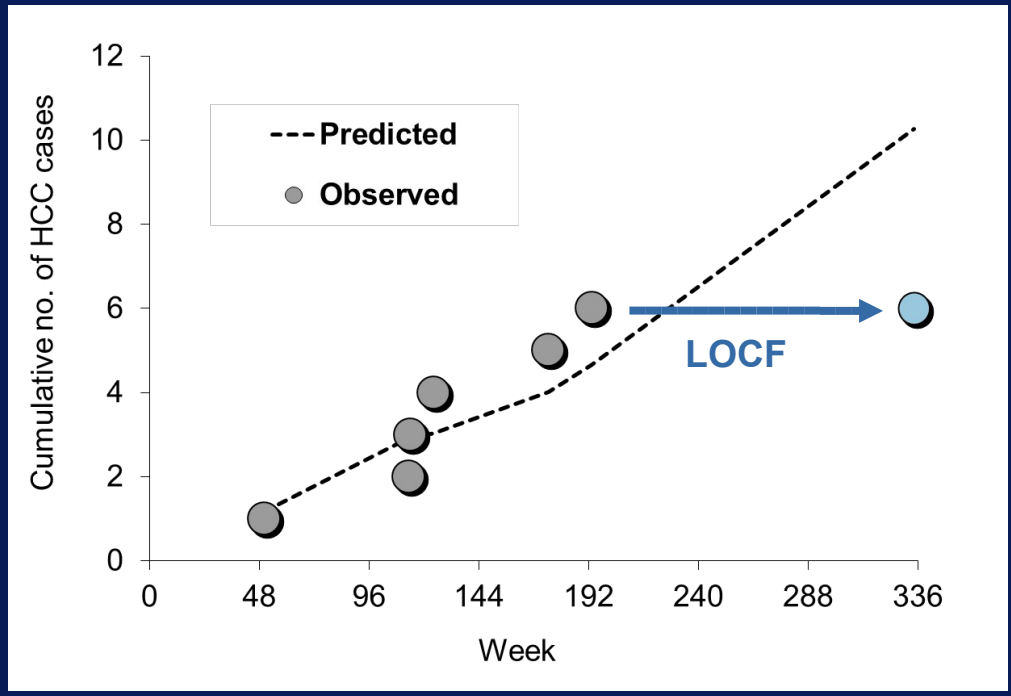
1. Wong, Gastroenterology 2013; 2. Hosaka, Hepatology 2013; 3. Lampertico, EASL 2013; 4. Lampertico AASLD 2013; 5. Papatheodoridis, AASLD 2013; 6. Fattovich, J Hepatol 2008

Long-term Tenofovir Disoproxil Fumarate Therapy And The Risk Of HCC (REACH-B)

Observed vs Predicted HCC Cases: non-cirrhotics



Observed vs Predicted HCC Cases: cirrhotics



*Statistically signif cant at nominal α-level of 0.05.
CI, conf dence interval; SIR, standardized incidence ratio.

LOCF= last observation carried forward.

W.R. Kim et al. J Hepatol 2013;58 Suppl 1:S19

The Clinical Benefits of Continuous NUC Therapy in HBV

- Universal access and HBV suppression, ~ 40% rates of *e-antigen* seroconversion, < 5% rates of HBsAg seroclearance
- High rates of prevention/reversal of both cirrhosis and clinical decompensation in both HBeAg(+) and HBeAg(-) patients
- Chemoprevention of HCC likely in cirrhosis, may be in chronic hepatitis patients

Factors Other Than Virus Replication Affecting HCC Risk in HBV Patients

Virus	Genotype(C)
	Pre-S mutations
	Enhancer-H mutations(T 1653)
	Core promoter mutations(V 1753,T 1762,A 1764)
Host	Increasing age
	Male gender
	Cirrhosis
Alcohol/Tobacco	
	Genetic polymorphisms (SNIPs)

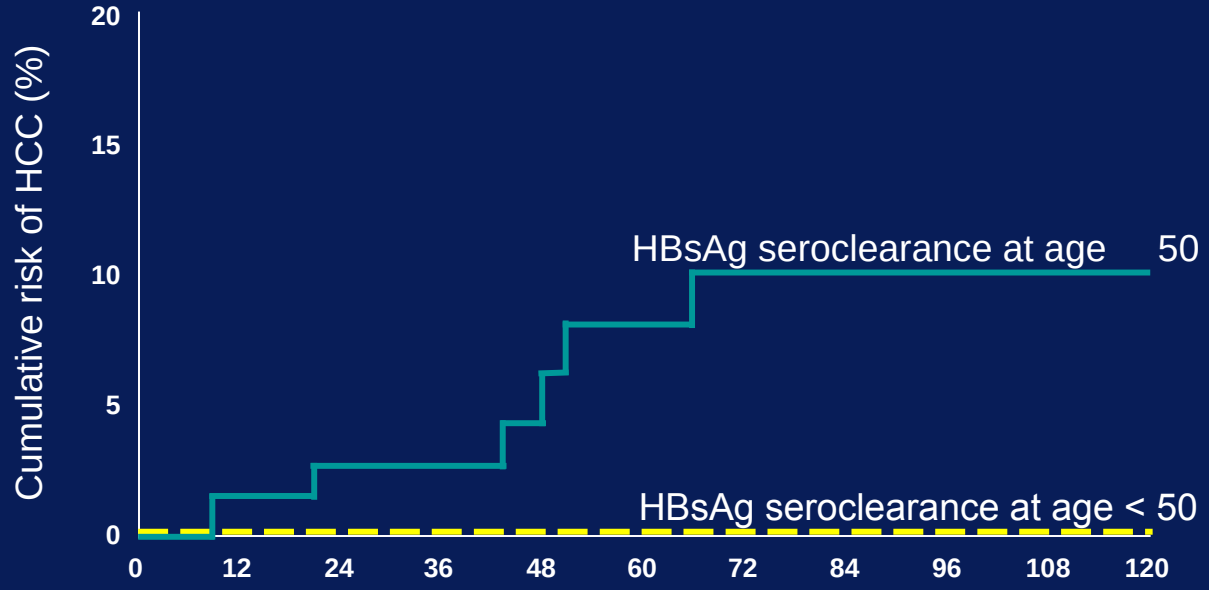
Yeung et al JID 2011;203:646-54; Yuen et al GUT 2008;57:98-102

Cumulative HCC Risk In Patients With HBsAg Clearance Aged < 50 And ≥ 50 Years[1]

Queen Mary Hospital, HK

1980–2006: 298 HBsAg seroconverters (95.6% spontaneous clearance)

1975–2001: 92 HBsAg seroconverters[2]



Age of HBsAg seroclearance												
No. of patients at risk	< 50	151	124	102	87	71	56	47	37	21	15	10
	50	147	120	86	63	51	46	38	31	24	18	12

1. Yuen MF, et al. Gastroenterology. 2008;135:1192–9.
2. Yuen MF, et al. Hepatology. 2004;39:1694–1701.

HCC Risk in Inactive Carriers of HBV: The REVEAL Study

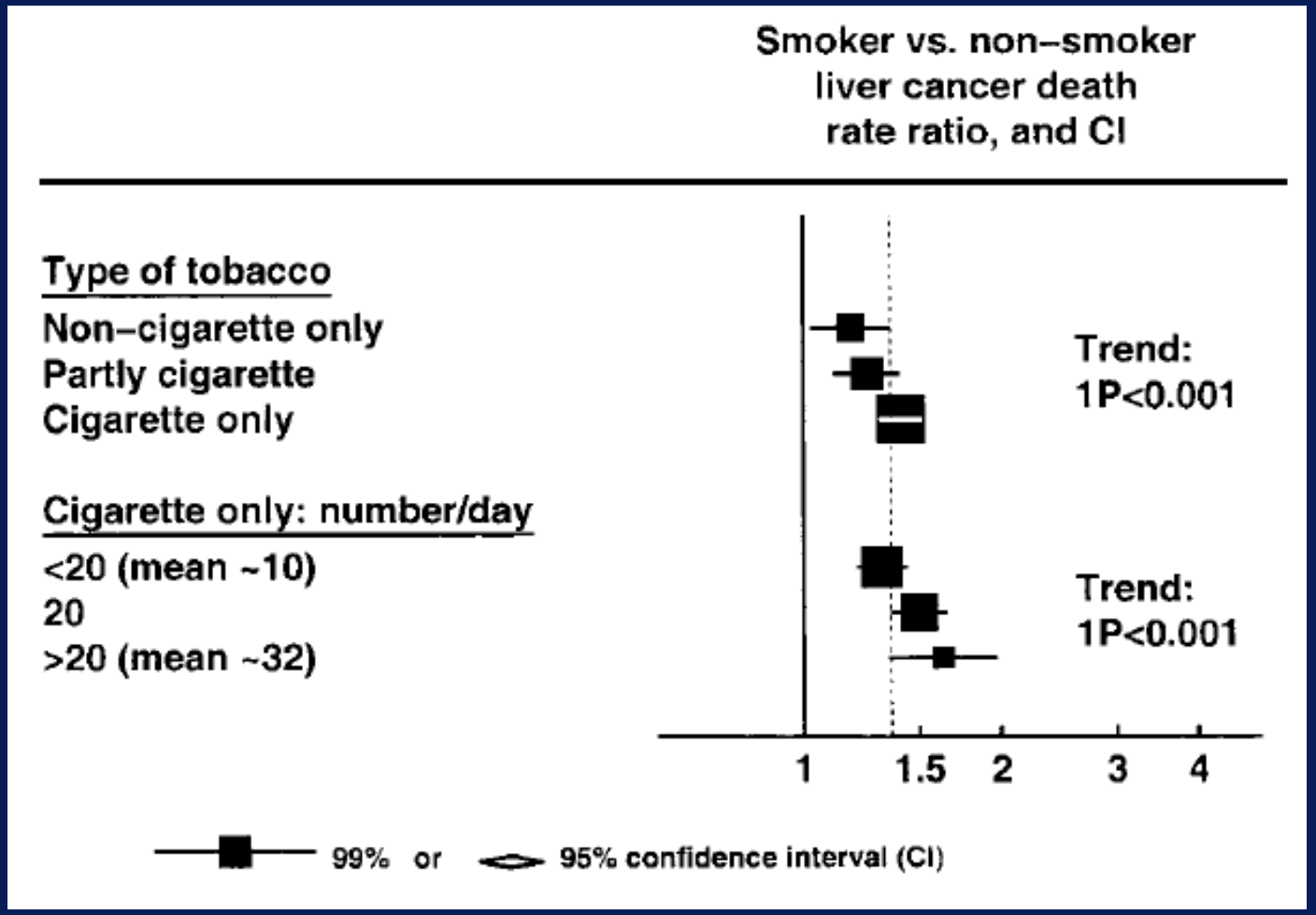
Inactive carriers	1,932	HBeAg neg, DNA < 2,000 IU, cirrhosis free
Controls	18,137	HBsAg neg, anti-HCV neg
Follow-up	13.1 years	
Outcomes	HCC x year LRM x year	0.06% vs 0.02%* (inactive carriers vs controls) 0.04% vs 0.02%** (inactive carriers vs controls)

HCC predictors	Older age Alcohol habits

*HR = 4.6 (95% CI 2.5–8.3); **HR = 2.1 (95% CI 1.5–2.9).

Chen et al. Gastroenterology 2010;138:1747-54.

Smoking and HCC in China: Case-Control Comparison 36,000 HCC Deaths vs. 17,000 Cirrhosis Deaths



Chen et al. Int J Cancer 2003;107:106-112

Obesity and Diabetes are Associated with an Increased Risk of HCC

- Evidence for obesity: large population studies in Europe, US and Taiwan[1–7]
- Evidence for diabetes: case-control studies, cohort studies } meta-analysis[8]

Modifying effect of hepatitis B/C on obesity and diabetes/HCC association[9]

In Taiwan > 100-fold increased risk of HCC in HBV or HCV carriers with both obesity and diabetes[9]

1. Moller, Eur J Cancer 1994. 2. Wolk, Cancer Causes Control 2001. 3. Rapp, Br J Cancer 2005. 4. Calle, N Engl J Med 2003. 5. Samanic, Cancer Causes Control 2004. 6. Nair , Hepatology 2002. 7. Lai, Hepatology 2006. 8. El-Serag, Clin Gastroenterol Hepatol 2006. 9. Chen, Gastroenterology 2008

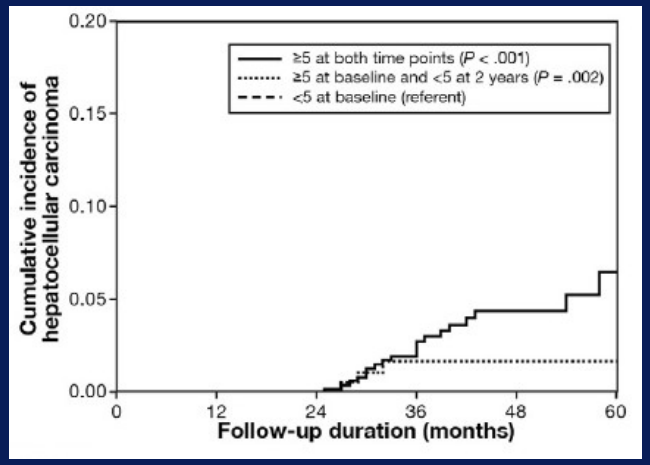
Genetic Associations With HCC In Patients With Chronic Hepatitis B Infection

Author	Study	Patients	#	SNP	Strenght OR (95% CI)
Zhang et al (2010)	GWAS	Chronic hepatitis HCC	1790 2317	KIF1b	0.6 (0.5-0.6)
Liu et al (2012)	SNP	Chronic hepatitis HBV neg HCC	1344 1344 1300	MCM7	1.2 (1.0-1.4)
Chan et al (2011)	GWAS	Chronic hepatitis HCC	825 595	DLC1	1.3 (n.a.)
Gu et al (2010)	SNP	Chronic hepatitis HBV neg HCC	209 419 375	CTLA-4	1.7 (1.0-3.0)
Chou et al (2008)	SNP	Chronic hepatitis HCC	316 154	EnhII/BCP Precore (C)	4.7 (2.1-10.5)
Ren et al (2012)	SNP	AVH Healthy controls HCC	43 47 154	IL28B (T)	6.1 (1.3-7.9)

R = retrospective study; GWAS = genome wide association study

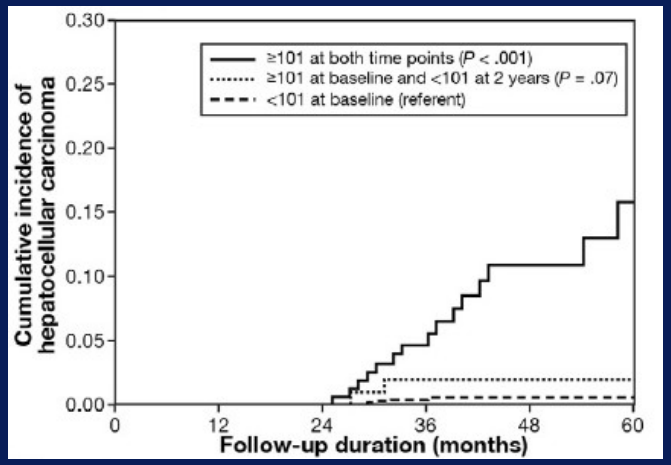
Risk Scores for HCC in HBV Patients Under Continuous Entecavir Treatment

CU-HCC



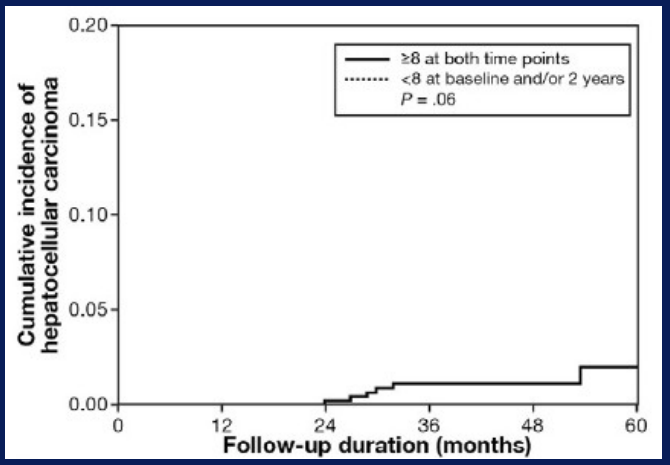
Age
Albumin
Bilirubin
HBV-DNA
Cirrhosis

GAG-HCC



Age
Gender
HBV-DNA
Core promoter mutations
Cirrhosis

REACH-B



Age
Gender
ALT
HBV-DNA
HBeAg

Wong et al, Gastroenterology 2013;144:933–944

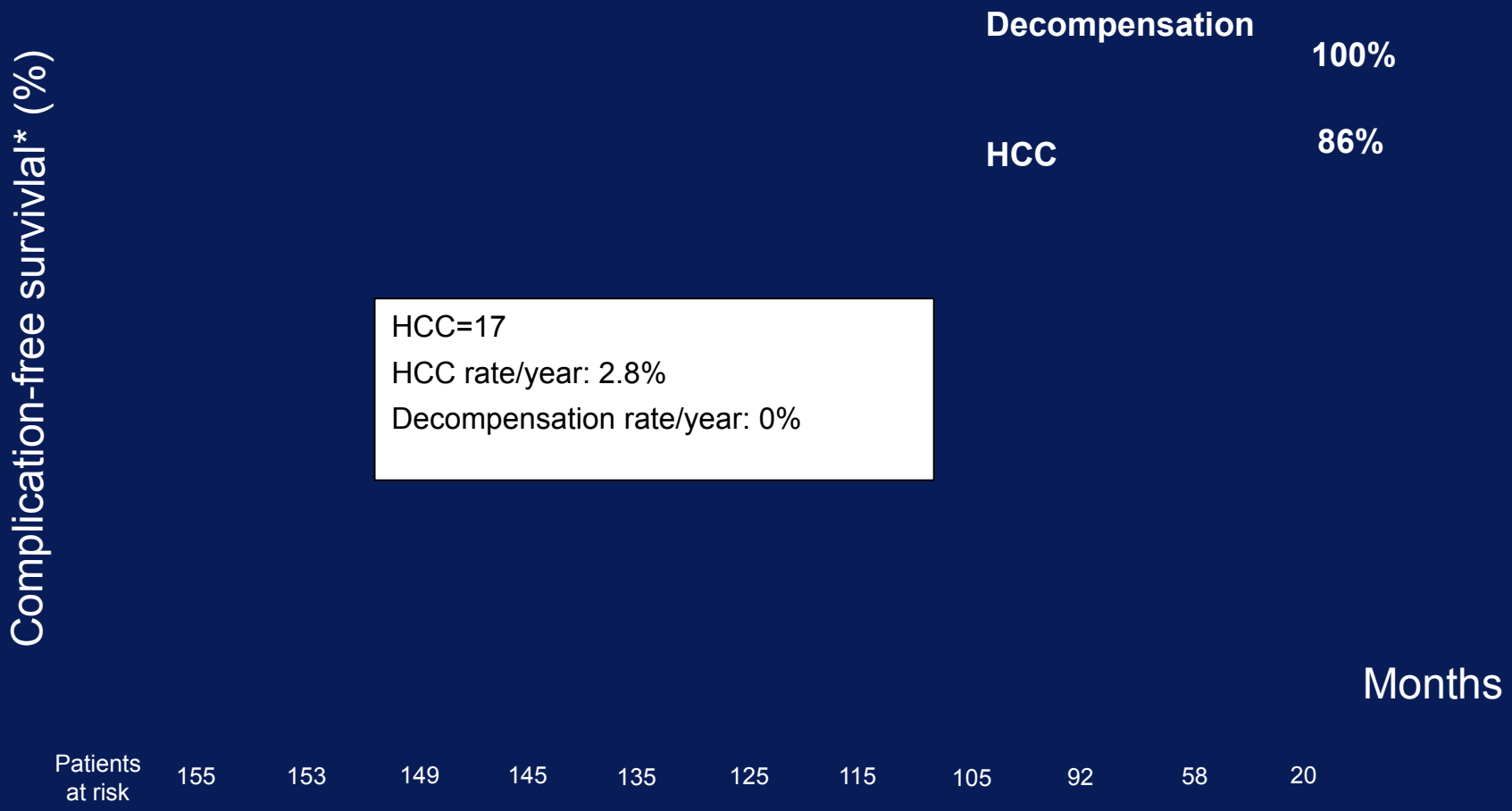
Take Home Message

1. Sustained suppression of HBV by either IFN-based or NUC regimens prevents progression of hepatitis B to end stage liver disease in responders.

2. This goal is achieved in 30% of responders to IFN based regimens (50% HBsAg seroclearance) and in virtually all patients treated with NUC (< 5% HBsAg seroclearance).

3. HCC risk is not eradicated by HBV treatment, thus responders need continuous US surveillance.

Incidence of Clinical Decompensation & HCC in Cirrhotics Under Entecavir Monotherapy



* Kaplan-Meier estimates

Lampertico P et al, Hepatology 2012;56:370A-371A

Predicting Cost Effectiveness of HCC Surveillance by Markov Modelling

Cost-effectiveness: a gain of life expectancy of ≥ 3 months with

a cost < US$ 50,000 for year of life saved

Surveillance is cost-effective:

HCC incidence ≥ 1.5% per year in cirrhotics[1]

HCC incidence ≥ 0.2% per year in HBV carriers[2]

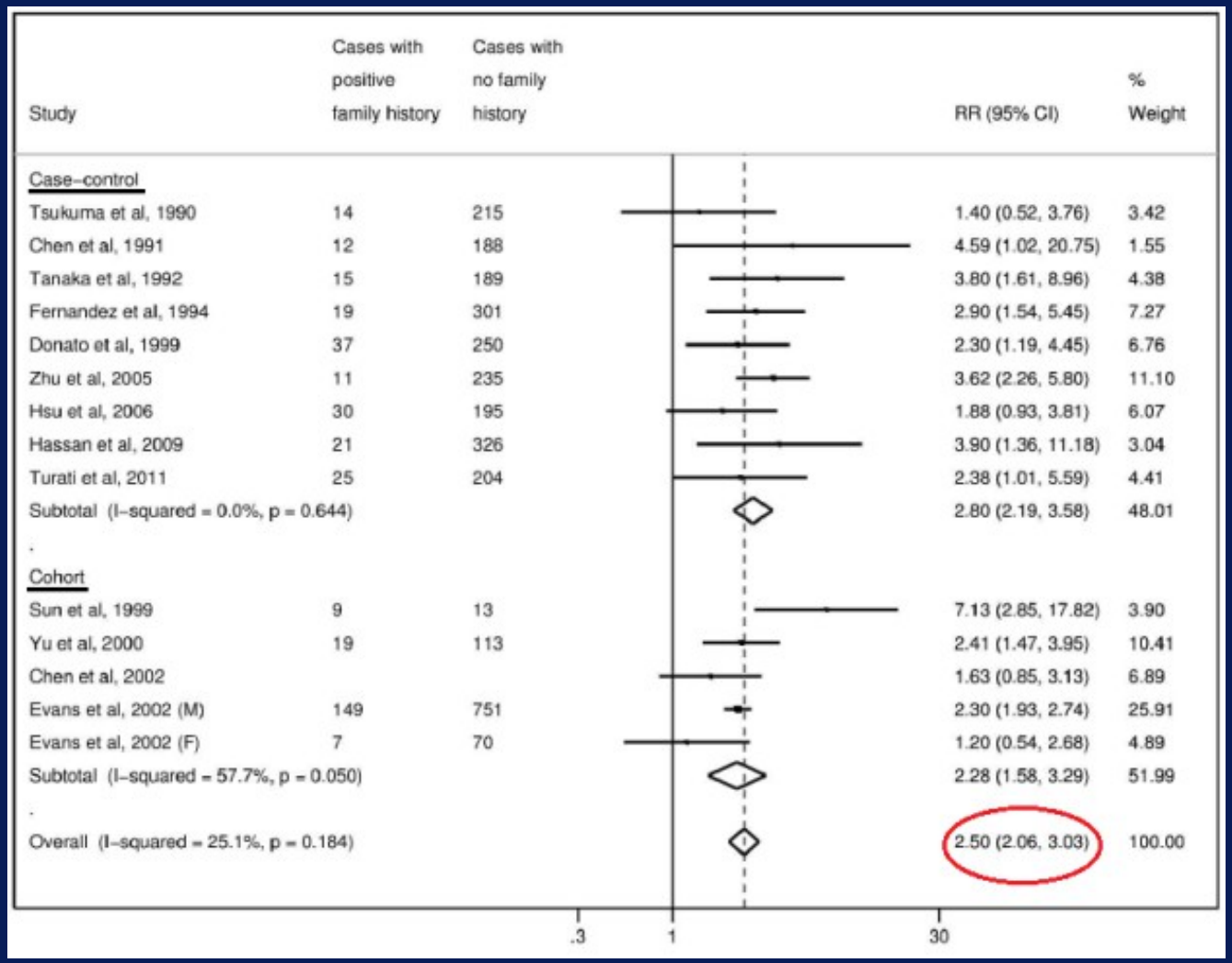
1. Sarasin et al, Am J Med 1996; 171:422-34. 2. Bruix & Sherman Hepatology 2011; 53:1021–2.

Histological Reversal of Viral Cirrhosis Following a Sustained Virological Response

Study	Etiology	Treatment	Months after SVR	Regressors #
Mallet (2008)	HCV	Peg/IFN+Rbv	11	17/39 (44%)
D'Ambrosio (2012)	HCV	Peg/IFN+Rbv	67	23/38 (61%)
Chang (2010)	HBV	ETV	72	4/10 (40%)
Marcellin (2011)	HBV	TDF	60	71/96 (74%)

Mallet et al, Ann Intern Med 2008;149:399-403. D'Ambrosio et al, Hepatology 2012:56:532-43. Chang et al Hepatology 2010;52:886-93. Marcellin et al, Hepatology 2011;54 suppl:1011A-1012A

Increased Risk of HCC in Patients with a Family History of Liver Cancer

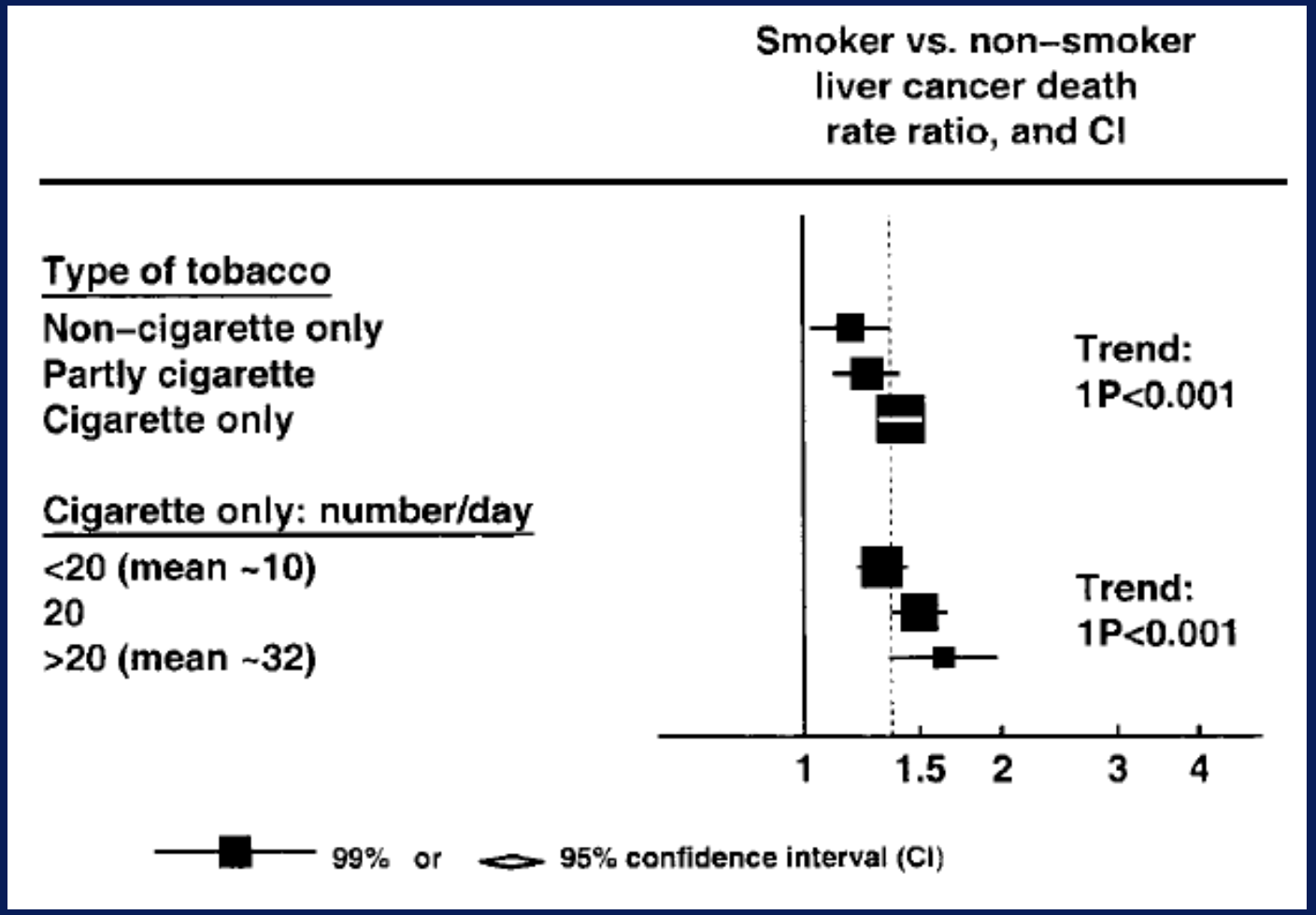


Study	Cases with positive family history	Cases with no family history	RR (95% CI)	% Weight
Case–control				
Tsukuma et al, 1990	14	215	1.40 (0.52, 3.76)	3.42
Chen et al, 1991	12	188	4.59 (1.02, 20.75)	1.55
Tanaka et al, 1992	15	189	3.80 (1.61, 8.96)	4.38
Fernandez et al, 1994	19	301	2.90 (1.54, 5.45)	7.27
Donato et al, 1999	37	250	2.30 (1.19, 4.45)	6.76
Zhu et al, 2005	11	235	3.62 (2.26, 5.80)	11.10
Hsu et al, 2006	30	195	1.88 (0.93, 3.81)	6.07
Hassan et al, 2009	21	326	3.90 (1.36, 11.18)	3.04
Turati et al, 2011	25	204	2.38 (1.01, 5.59)	4.41
Subtotal (I–squared = 0.0%, p = 0.644)			2.80 (2.19, 3.58)	48.01
Cohort				
Sun et al, 1999	9	13	7.13 (2.85, 17.82)	3.90
Yu et al, 2000	19	113	2.41 (1.47, 3.95)	10.41
Chen et al, 2002			1.63 (0.85, 3.13)	6.89
Evans et al, 2002 (M)	149	751	2.30 (1.93, 2.74)	25.91
Evans et al, 2002 (F)	7	70	1.20 (0.54, 2.68)	4.89
Subtotal (I–squared = 57.7%, p = 0.050)			2.28 (1.58, 3.29)	51.99
Overall (I–squared = 25.1%, p = 0.184)			2.50 (2.06, 3.03)	100.00

.3 1 30

Turati et al. Hepatology 2012;55:1416-25

Smoking and HCC in China: Case-Control Comparison 36,000 HCC Deaths vs. 17,000 Cirrhosis Deaths



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Camma et al 2001[1]	**7**	853 vs 652	4.8%* (0.11 – 0.015)	NS	No effects in Europeans
Zhang et al 2011[5]	2	176 vs 171	0.23 (0.05 – 1.04)	NS	Small sample size
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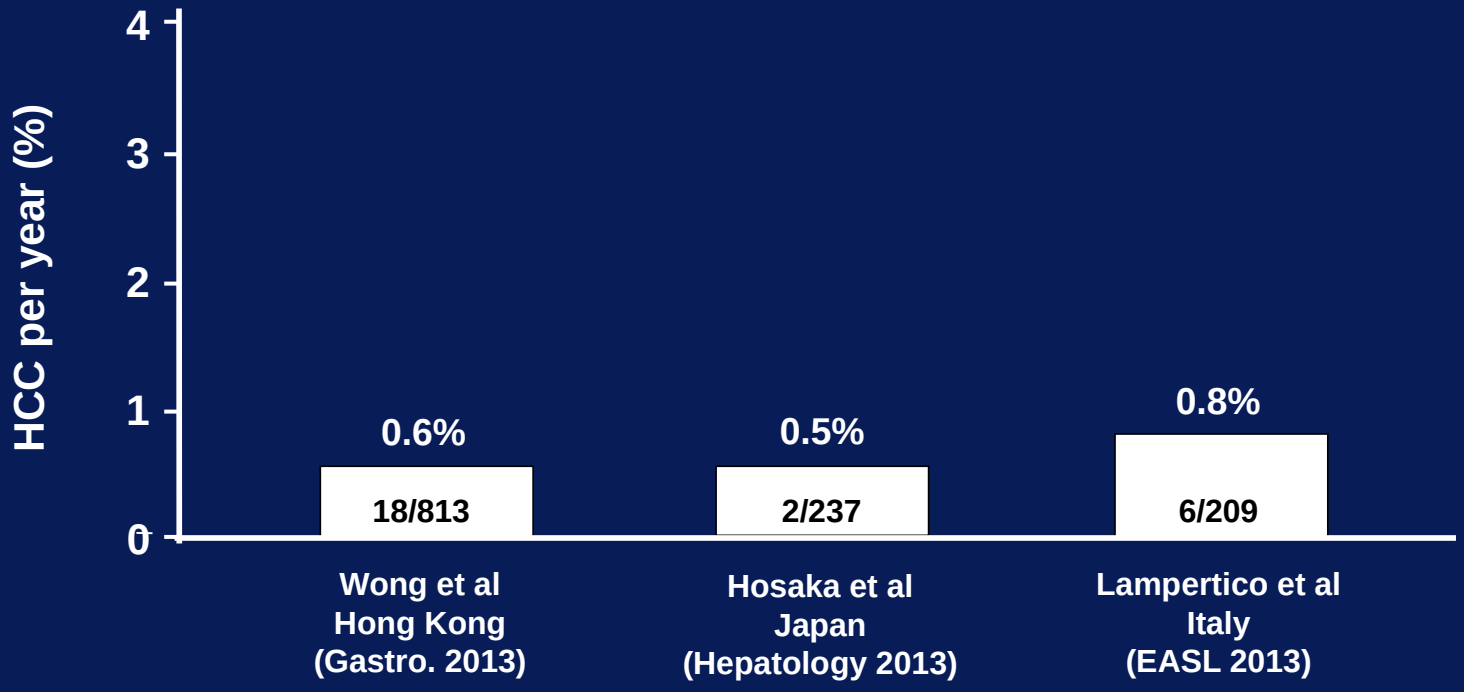
1. Camma et al. J Hepatol 2001;34:593-602. 2. Miyake Y et al. J Gastroenterol 2009;44:470-5. 3. Sung JJ, et al. Aliment Pharmacol Ther 2008;28:1067-77. 4. Yang YF et al. J Viral Hepat 2009;16:265-71. 5. Zhang CH et al. Int J Cancer 2011;129:1254-64. 6. Jin H et al. Hepatol Res 2011;41:512-23.

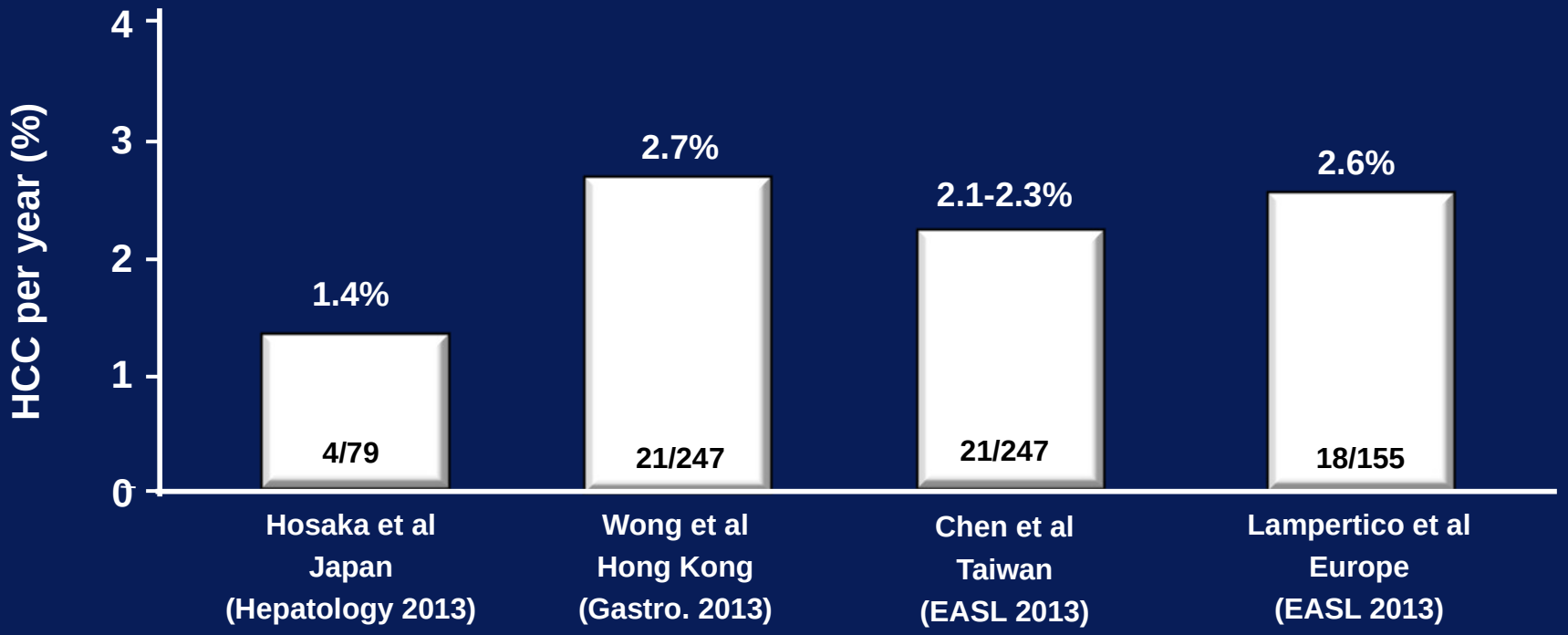
Duration of ETV Therapy: 4-6 Years



HCC/yr in <u>untreated</u> CHB patients: 0.6% (Asia) and 0.3% (Europe)

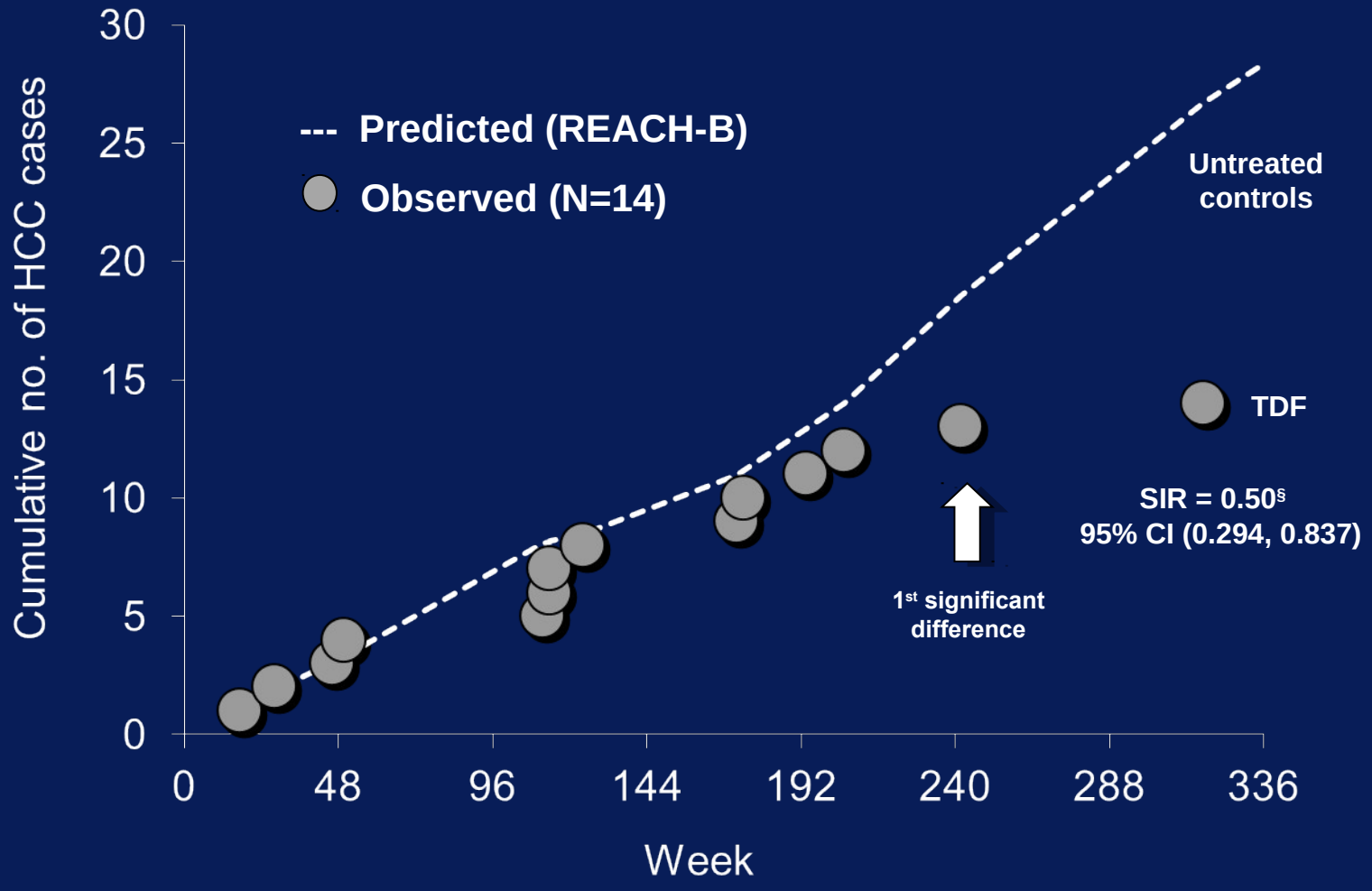
(Fattovich G et al, J Hepatol 2008)

Development of HCC in Cirrhotic HBV Patients Under Continuous ETV Therapy



HCC/yr in <u>untreated</u> cirrhotics: 3.7% (Asia) and 2.2% (Europe)

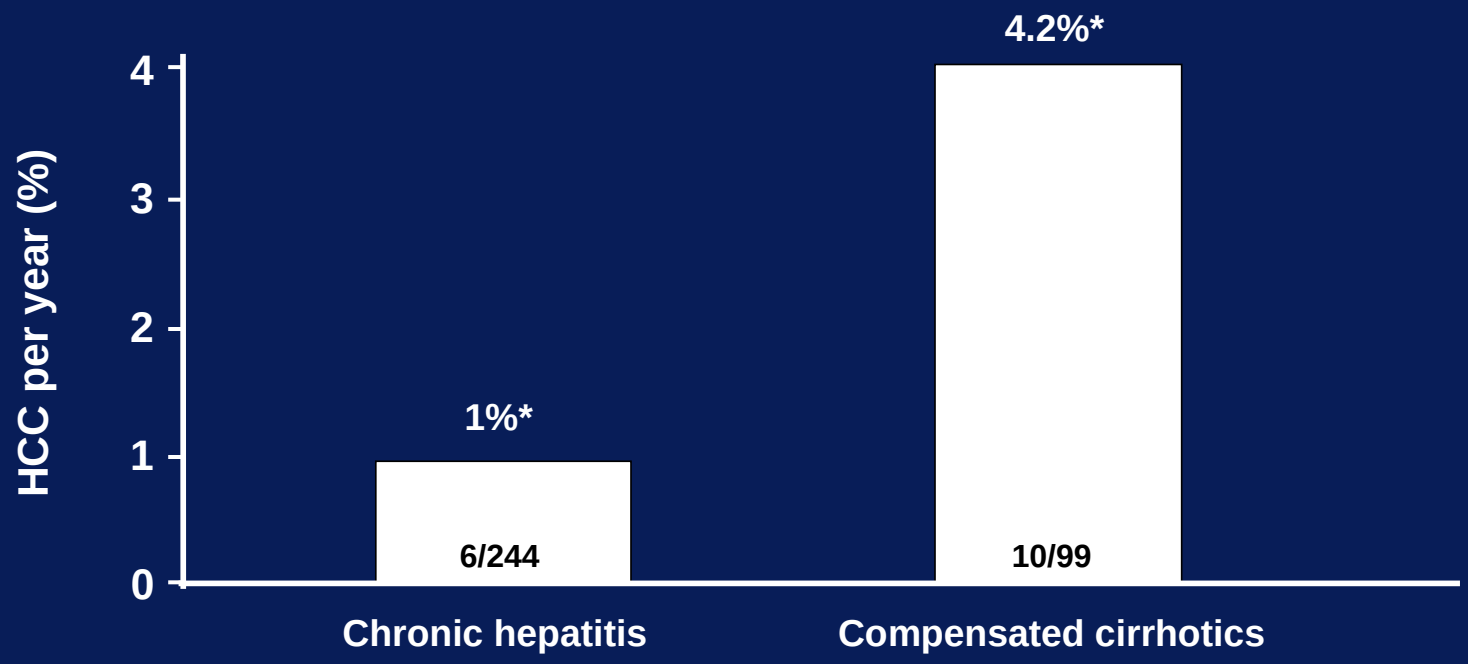
(Fattovich G et al, J Hepatol 2008)



Kim R et al, EASL 2013

*Statistically significant at nominal α-level of 0.05.
SIR, standardized incidence ratio.

Duration of ETV Therapy: 4-6 Years



HCC/yr in Europe: 0.3% (CHB) and 2.2 % (cirrhosis)

(Fattovich G et al, J Hepatol 2008)

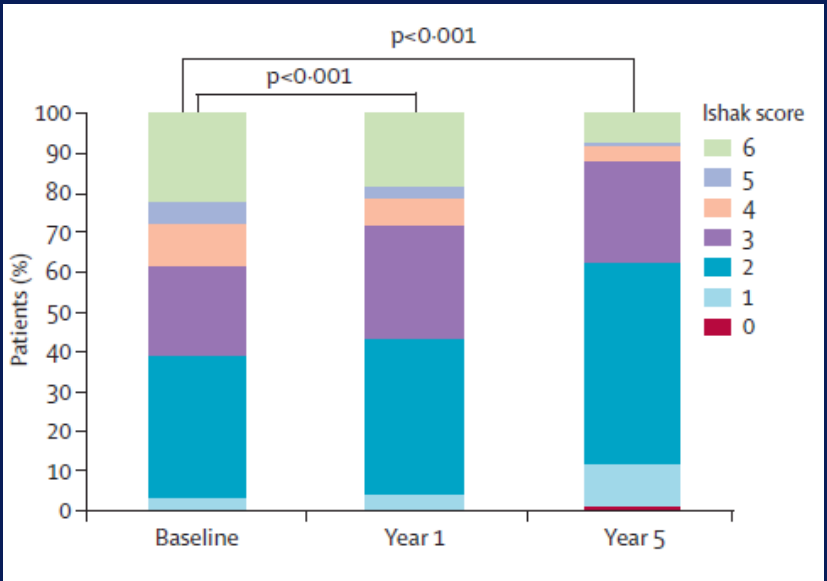
Lampertico P et al, AASLD 2013

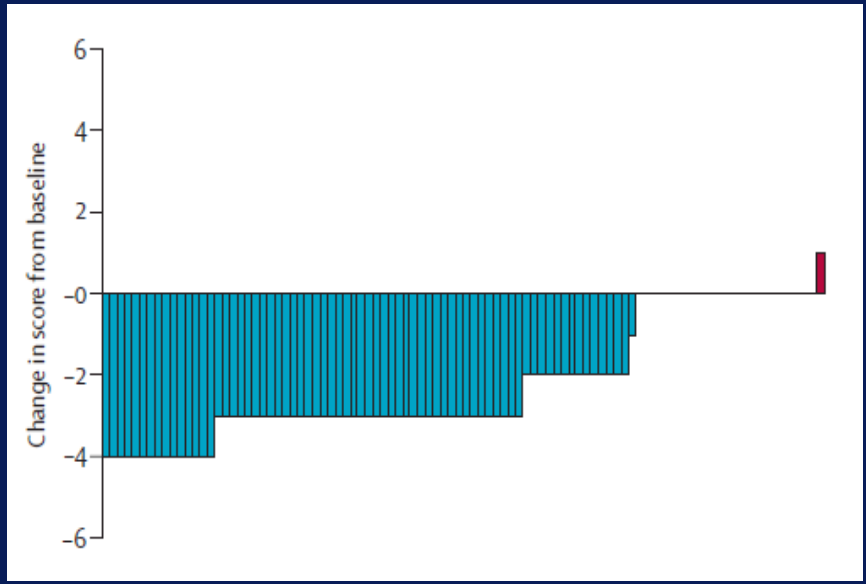
***Estimated rates by KM analysis**

Five-year TDF Treatment in Patients with CHB
Changes of Fibrosis in Cirrhotics

96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and year 5 biopsies

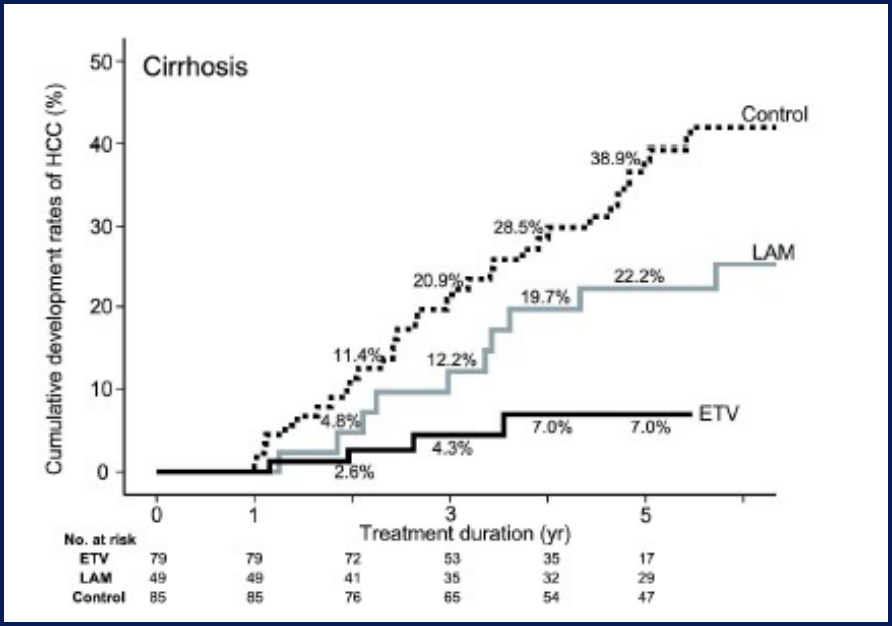
71 (74%) had cirrhosis reversed (Ishak fibrosis score <5) at Year 5

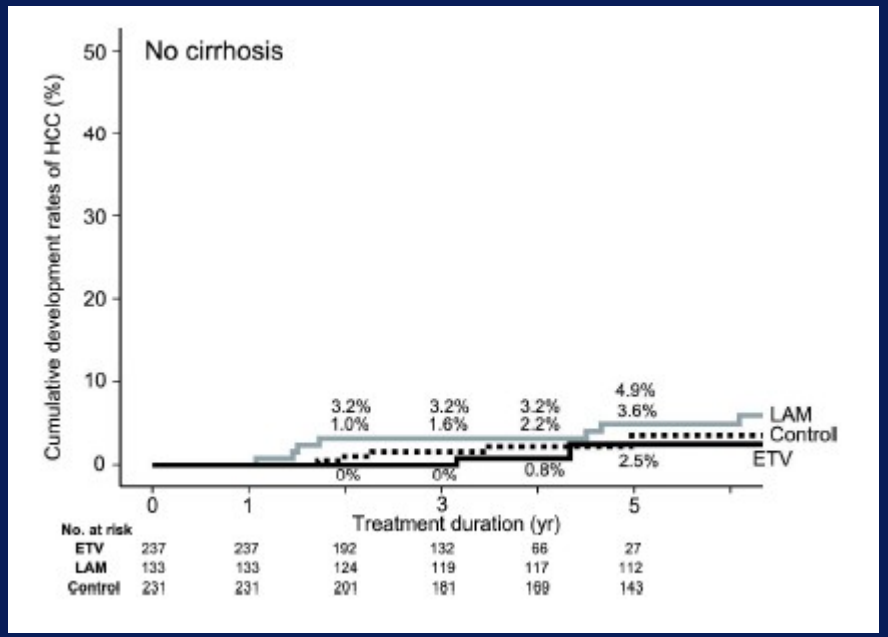




Marcellin et al, Lancet 2013;381:468-75

Long-term Entecavir Treatment Reduces HCC Incidence in Patients With Hepatitis B Virus Infection





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

Predicting Cost Effectiveness of HCC Surveillance by Markov Modelling

Cost-effectiveness: a gain of life expectancy of ≥ 3 months with

a cost < US$ 50,000 for year of life saved

Surveillance is cost-effective:

HCC incidence ≥ 1.5% per year in cirrhotics[1]

HCC incidence ≥ 0.2% per year in HBV carriers[2]

1. Sarrazin et al, Am J Med 1996; 2. Bruix & Sherman Hepatology 2011

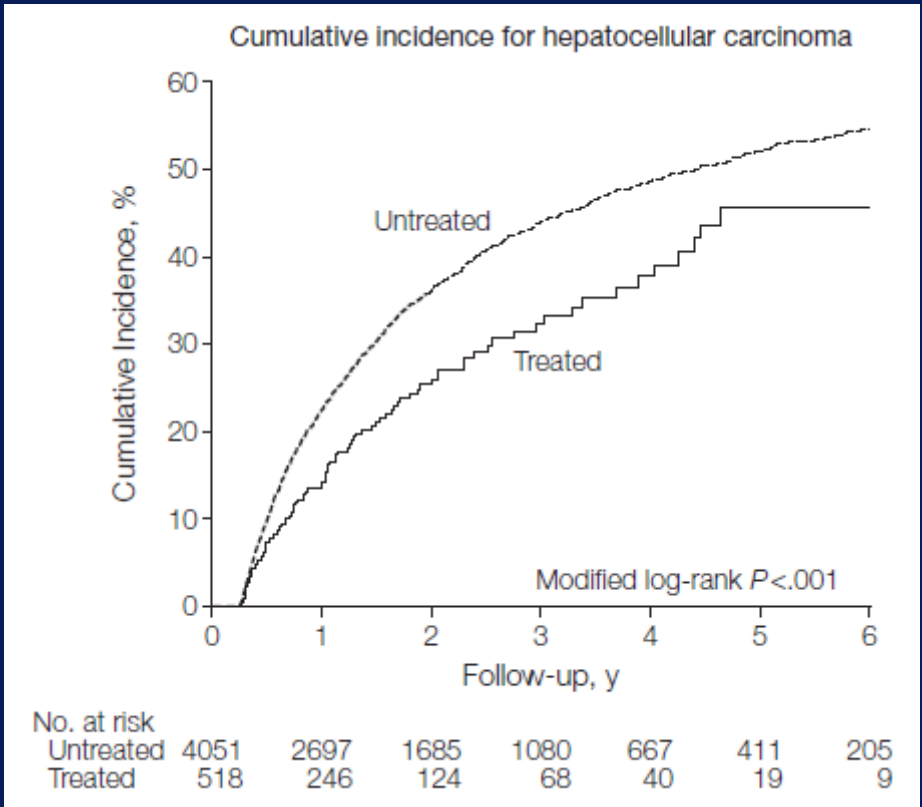
Predicting Cost-Effectiveness of Surveillance by Markov Modeling

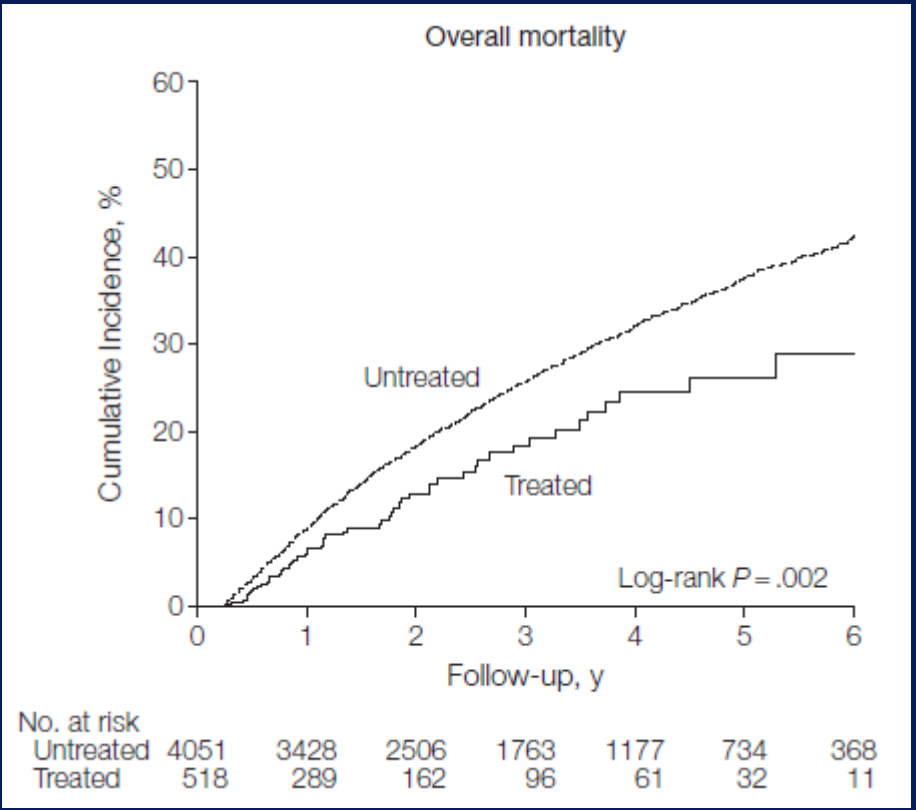
Surveillance recommended		
Population group	**Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)**	**Incidence of HCC**
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

Bruix J, Sherman M. Management of Hepatocellular Carcinoma, an Update. www.aasld.org/practiceguidelines/pages/default .aspx

Association Between NUC and Risk of HBV–Related HCC Recurrence Following Liver Resection

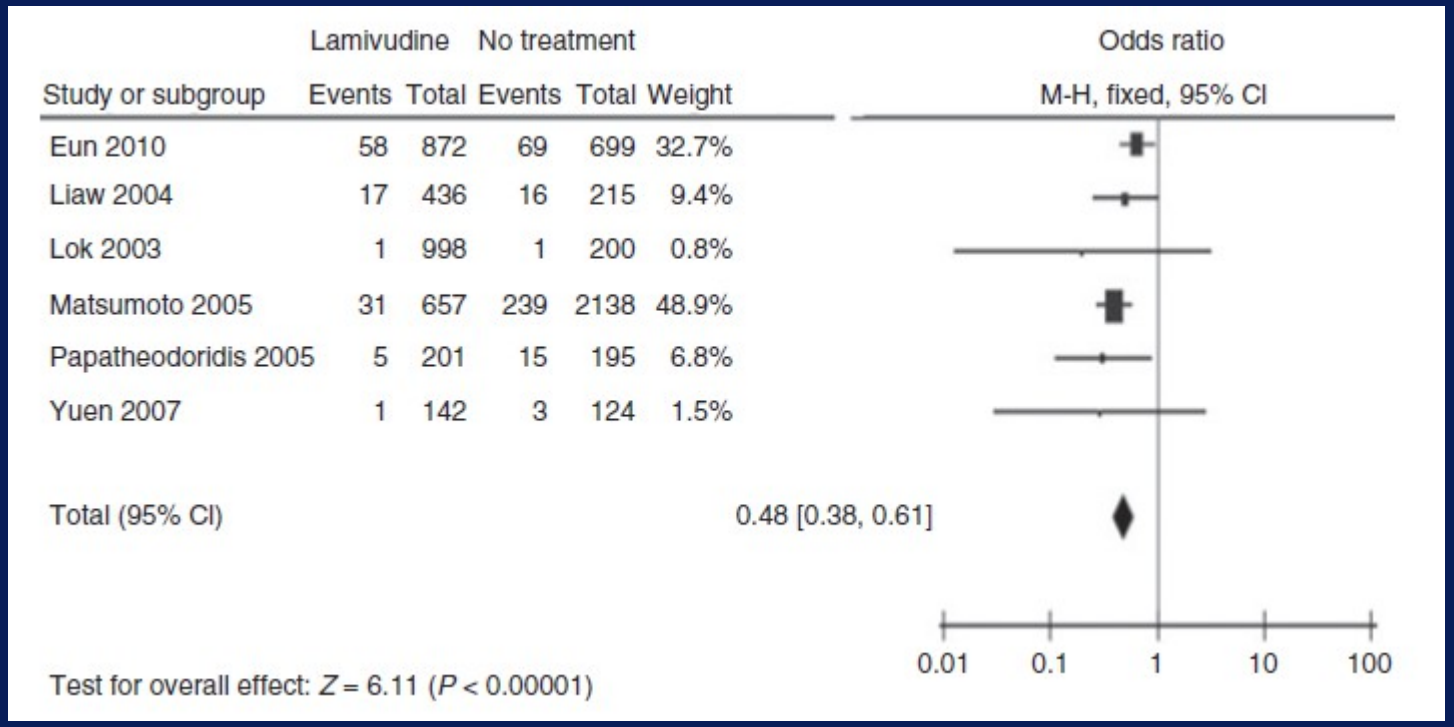
Cumulative Incidences of HCC Recurrence and Overall Mortality Following Liver Resection





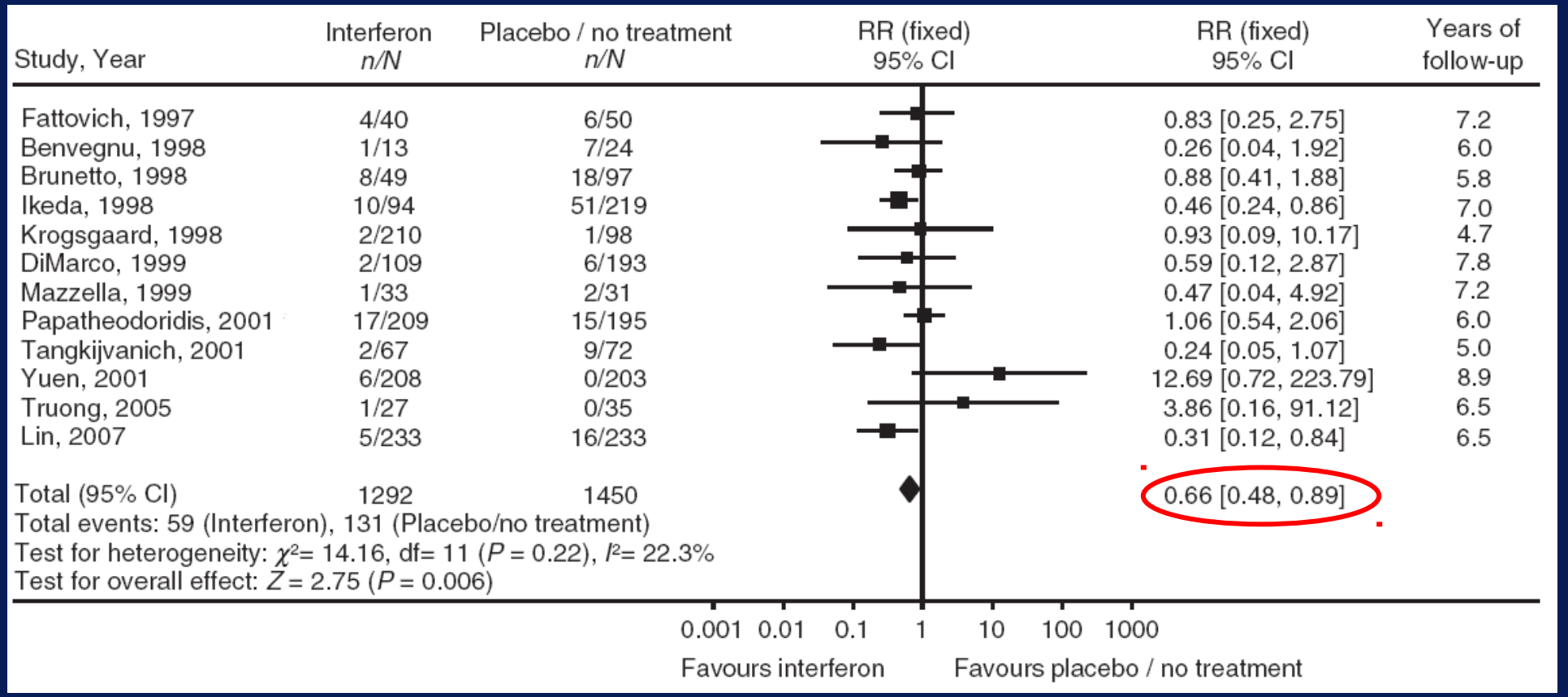
Wu et al, JAMA 2013;308:1906-14

Meta-analysis: The Impact of Oral Anti-viral Agents on the Incidence of HCC in Chronic Hepatitis B



Singal et al, AP&T 2013;38:99-106

Meta-analysis of 12 Controlled Trials of IFN Therapy in Patients with HBV Cirrhosis: The Risk of HCC



Sung JJY et al Alim Pharmacol Ther 2008;28:1067-1077

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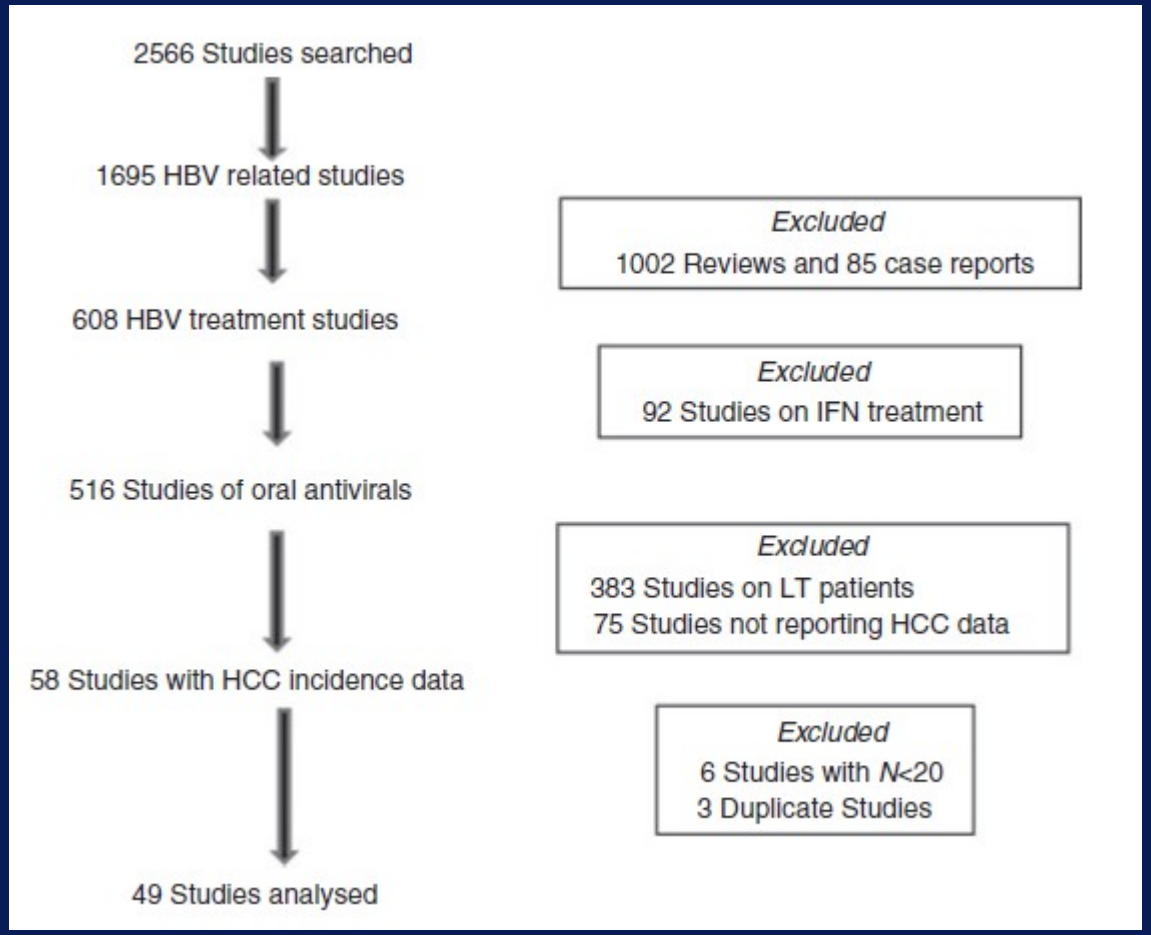

Singal et al, AP&T 2013;38:99-106

Seroclearance of HBV DNA Predicts Significantly Reduced Risk of HCC Among Those with High Viral Loads: a Time-dependent Analysis of Serially Measured Biomarkers

REVEAL: ~ 3000 non-cirrhotics (30-65 yr) 7 townships Taiwan 1991
Since 2004 screening every 6/12 mo, 153 HCCs
Antiviral therapy?

MAHR for HCC	All (N=2946)		HBV DNA detectable (N=2191)		HBeAg Seropositive (N=444)	
	Multivariate Adjusted HR (95% CI)	P-Value	Multivariate Adjusted HR (95% CI)	P-Value	Multivariate Adjusted HR (95% CI)	P-Value
HBsAg seroclearance						
Yes vs. No	0.63 (0.29-1.38)	0.25	--		--	
HBV DNA decreased to undetectable						
Yes vs. No	--		0.37 (0.16-0.86)	0.02	--	
HBeAg Seroclearance						
Yes vs. No	--		--		0.97 (0.56-1.69)	0.92

*also adjusted for age, gender, smoking, alcohol consumption, ALT level, HBeAg serostatus, and HBV DNA levels

J. Liu et al. Abstract 40

	1005 in training cohort, 424 in validation cohort	bilirubin, HBV DNA, cirrhosis		10 years
GAG-HCC	820 clinic patients (leave-one-out cross-validation method)	Age, gender, HBV DNA, cirrhosis	101	99% NPV at 10 years
REACH-B	Non-cirrhotic patients: 3584 in training cohort, 1505 in validation cohort	Age, gender, ALT, HBV DNA, HBeAg	8	98% NPV at 10 years

Score	Patients	Components	Cutoff	Performance
CU-HCC		Age, albumin, bilirubin,	5	97% NPV at 10 years
GAG-HCC			101	99% NPV at 10 years
REACH-B			8	98% NPV at 10 years

Wong VW et al. J Clin Oncol 2010;28:166. Yuen MF et al. J Hepatol 2009;50:80. Yang HI et al. Lancet Oncol 2011;12:568

Risk Scores For Hbv-related HCC

Score	Patients	Components	Cutoff	Performance
CU-HCC	Clinic patients: 1005 in training cohort, 424 in validation cohort	Age, albumin, bilirubin, HBV DNA, cirrhosis	5	97% NPV at 10 years
GAG-HCC	820 clinic patients (leave-one-out cross-validation method)	Age, gender, HBV DNA, cirrhosis	101	99% NPV at 10 years
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Wong VW et al. J Clin Oncol 2010;28:166. Yuen MF et al. J Hepatol 2009;50:80. Yang HI et al. Lancet Oncol 2011;12:568

Performance Of HCC Risk Scores In Chronic Hepatitis B Patients Receiving Entecavir Treatment

Patient characteristics

N	1531
Age (years)	51
Male gender	72%
Albumin (g/l)	44
Bilirubin (µmol/l)	23
ALT (IU/l)	147
HBV DNA (log IU/ml)	5.0
Positive HBeAg	30%
Cirrhosis	22%
Follow-up duration (months)	42
HCC	47 (3.1%)

V. Wong et al. Abstract 44

Performance Of HCC Risk Scores In Chronic Hepatitis B Patients Receiving Entecavir Treatment

	CU-HCC	GAG-HCC	REACH-B
Cutoffs	5	101	8
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%

V. Wong et al. Abstract 44

Long-term Tenofovir Disoproxil Fumarate Therapy And The Risk Of HCC (REACH-B)

Characteristic*	Cirrhotic (n=152)	Noncirrhotic (n=482)
Mean age, years (SD)	45.2 (10.6)	38.4 (11.8)
Male, n (%)	123 (81)	345 (72)
Race, n (%)		
White	92 (61)	283 (59)
Asian	39 (26)	148 (31)
Other	21 (13)	51 (10)
HBeAg positive, n (%)	60 (40)	283 (59)
Mean HBV DNA, $\log_{10}$ copies/mL (SD)	7.6 (1.4)	7.7 (1.5)
Mean ALT, U/L (SD)	143.2 (123.4)	143.0 (113.1)
HBV genotype		
A	34 (23)	67 (14)
B	10 (7)	64 (14)
C	27 (18)	83 (18)
D	73 (49)	239 (51)
Other	4 (3)	20 (4)

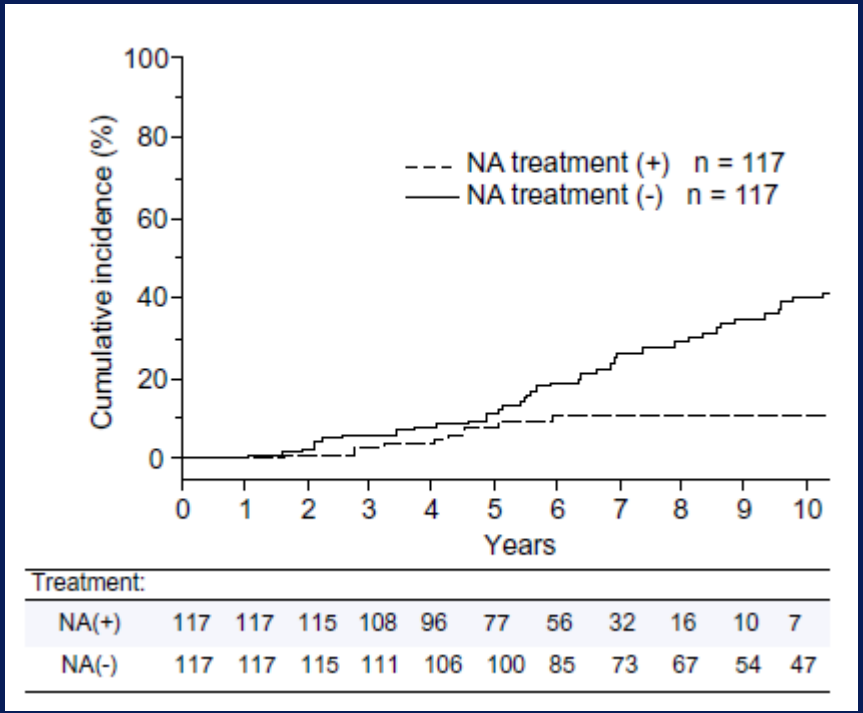
W.R. Kim et al. Abstract 43

HCC Risk In HBeAg-negative Patients On Long-term Entecavir

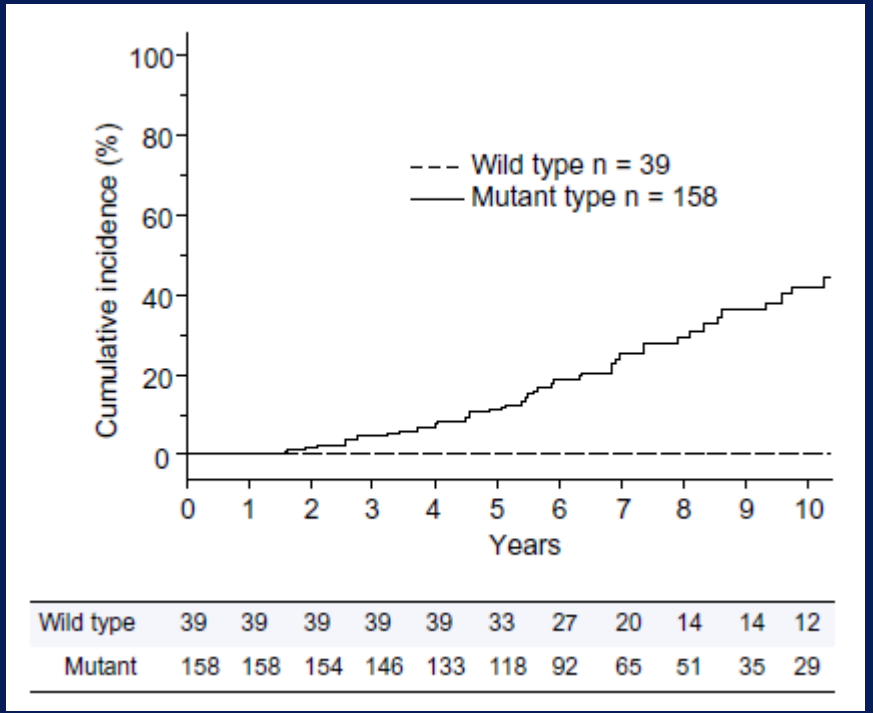
					HCC/yr, cirrhosis	
Authors	Abstract	Patients	Cirrhotics	Fup (mo)	Treated	Untreated
Lampertico	755	418	155	52 (2-66)	2.8%	-
Papatheodoridis	766	321	69	30±18	2.6%	-
Chen§	521	706/196	706/196	36±19	2.3%	5.7%*

§retrospective cohort study. Controls were historical untreated patients
*p=0.019

NUC Therapy on HCC Development in Chronic Hepatitis B
A Propensity Score Analysis



Treatment:											
NA(+)	117	117	115	108	96	77	56	32	16	10	7
NA(-)	117	117	115	111	106	100	85	73	67	54	47



Wild type	39	39	39	39	39	33	27	20	14	14	12
Mutant	158	158	154	146	133	118	92	65	51	35	29

Kumada et al, J Hepatol 2013;58:427-433

Effect of NUC Therapy on HCC in Chronic Hepatitis B Patients: A Propensity Score Analysis

Factors associated with progression to hepatocellular carcinoma among propensity-matched patients (Cox proportional hazard model).

		Adjusted hazard ratio (95% CI)	P-value
Age (yr)	≤40	1	0.015
	>40	4.36 (1.33-14.29)	
Treatment	No NA	1	0.002
	NA	0.28 (0.13-0.62)	
BCP	Wild-type	1	0.012
	Mutant-type	12.74 (1.74-93.11)	
HBcrAg (log_{10} U/ml)	≤3.0	1	0.036
	>3.0	2.77 (1.07-7.17)	
γ-GTP (IU/L)	≤56	1	0.001
	>56	2.76 (1.49-5.12)	

Kumada et al, Journal of Hepatology 2013;58:427-433

Association Between NUC and Risk of HBV–Related HCC Recurrence Following Liver Resection

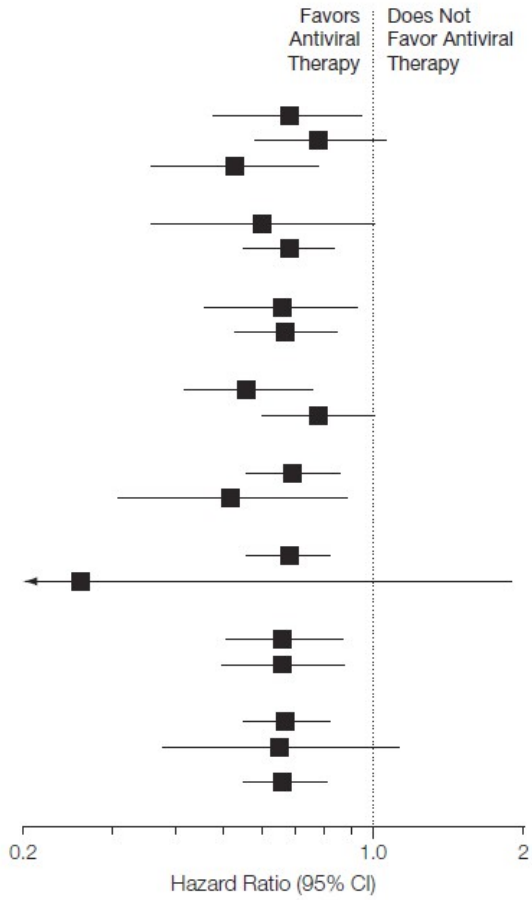
	No.	HCC Recurrence No.	HR (95% CI)	*P* Value
Treated vs untreated				
Untreated	4051	1765	1 [Reference]	
Treated	518	106	0.67 (0.55-0.81)	<.001
Age				
<50 y	1568	655	1 [Reference]	
50-59 y	1466	590	0.96 (0.83-1.10)	.53
≥60 y	1535	626	1.01 (0.90-1.13)	.92
Sex				
Women	799	306	1 [Reference]	
Men	3770	1565	1.08 (0.95-1.23)	.22
Resection				
Minor	2999	1228	1 [Reference]	
Major	1570	643	1.04 (0.90-1.20)	.61
Liver cirrhosis				
No	2748	1046	1 [Reference]	
Yes	1821	825	1.21 (1.04-1.40)	.01
Diabetes				
No	3834	1554	1 [Reference]	
Yes	735	317	1.18 (0.99-1.41)	.07
Statin use				
No	4394	1814	1 [Reference]	
Yes	175	57	0.68 (0.53-0.87)	.002
NSAID or aspirin use				
No	2117	932	1 [Reference]	
Yes	2452	939	0.80 (0.73-0.88)	<.001
Metformin use				
No	4011	1634	1 [Reference]	
Yes	558	237	1.01 (0.84-1.21)	.92
Propensity score				
Each incremental 10%	4569	1871	1.05 (0.78-1.41)	.74

Wu et al, JAMA 2013;308:1906-14

Association Between NUC and Risk of HBV–Related HCC Recurrence Following Liver Resection

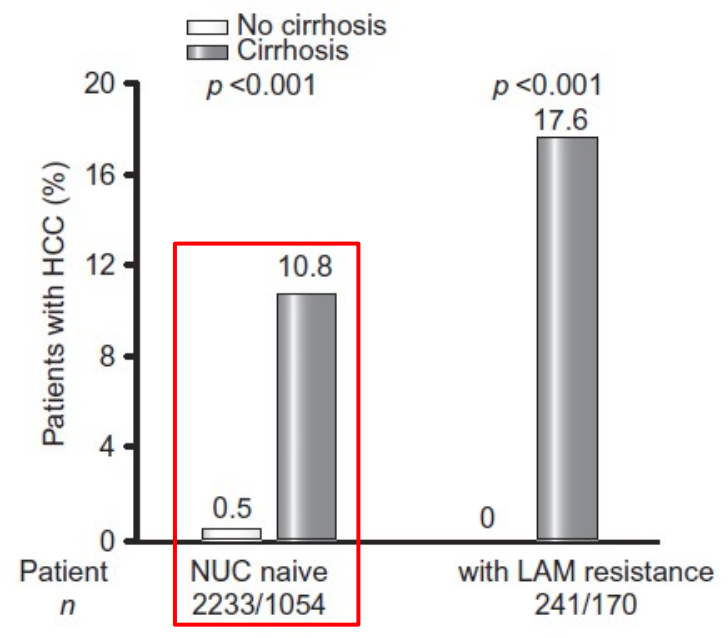
Multivariable Stratified Analyses for the Association Between Nucleoside Analogue Use and HCC Recurrence

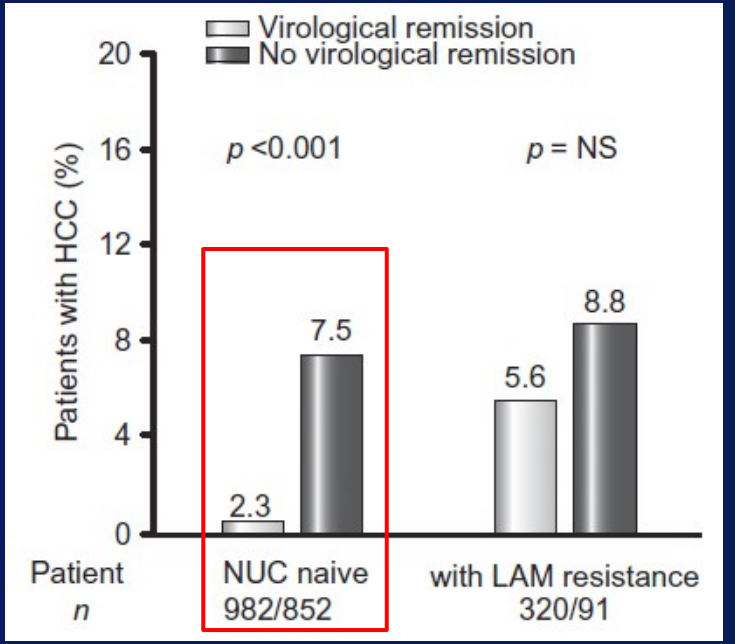
Subgroup	Untreated, No. Patients	Untreated, No. Recurrence	Treated, No. Patients	Treated, No. Recurrence	Hazard Ratio (95% CI)
Age, y					
<50	1418	619	150	36	0.68 (0.48-0.95)
50-59	1267	546	199	44	0.78 (0.58-1.06)
≥60	1366	600	169	26	0.53 (0.36-0.78)
Sex					
Male	716	291	83	15	0.60 (0.36-1.01)
Female	3335	1474	435	91	0.68 (0.55-0.84)
Resection					
Major	1431	612	139	31	0.66 (0.46-0.93)
Minor	2620	1153	379	75	0.67 (0.53-0.85)
Cirrhosis					
No	2482	1000	266	46	0.56 (0.42-0.76)
Yes	1569	765	252	60	0.78 (0.60-1.01)
Diabetes					
No	3388	1462	446	92	0.69 (0.56-0.86)
Yes	663	303	72	14	0.52 (0.31-0.89)
Statin					
No	3893	1709	501	105	0.68 (0.56-0.82)
Yes	158	56	17	1	0.26 (0.04-1.89)
NSAIDs or aspirin					
No	1870	878	247	54	0.66 (0.51-0.87)
Yes	2181	887	271	52	0.66 (0.50-0.88)
Metformin					
No	3553	1540	458	94	0.67 (0.55-0.82)
Yes	498	225	60	12	0.65 (0.38-1.13)
Overall	4051	1765	518	106	0.66 (0.55-0.81)



Wu et al, JAMA 2013;308:1906-14

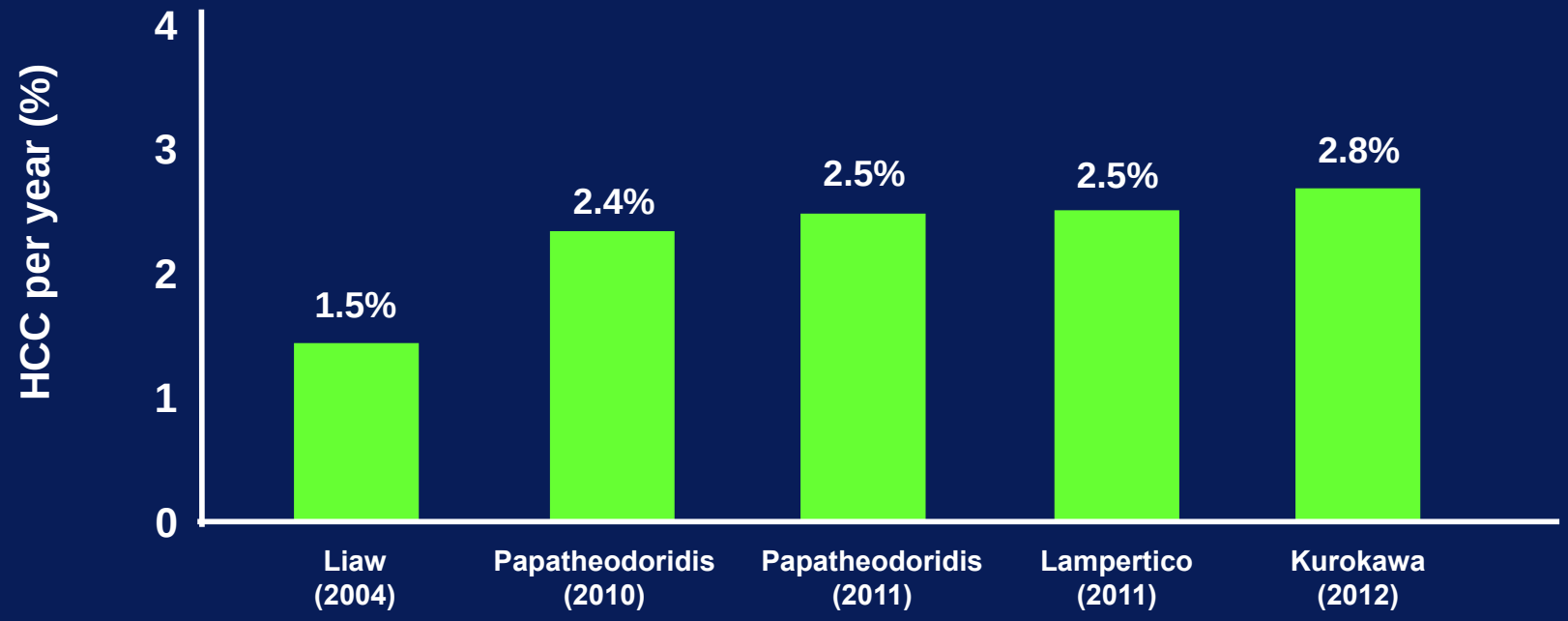
Incidence of HCC in Chronic HBV Patients Receiving Nucleos(t)ide Therapy: a Systematic Review





Papatheodoridis, et al. J Hepatol 2010;53:348-356

HCC Rates In Nucleos(t)ide Analogs (NUC)-naïve Cirrhotic Patients Long-term Responding To NUC



No Patients	211	81	62	164	42
Drug	LAM	LAM	LAM	ETV	LAM
Study	RCT	Review	Retrospective	Cohort prospective	Retrospective
Follow-up	3 yrs	2 yrs	6 yrs	4 yrs	5 yrs

Aghemo A et al. J Hepatol 2012;57:1326–35

Predicting Cost Effectiveness of HCC Surveillance by Markov Modelling

Cost-effectiveness: a gain of life expectancy of ≥ 3 months with

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Surveillance is cost-effective:

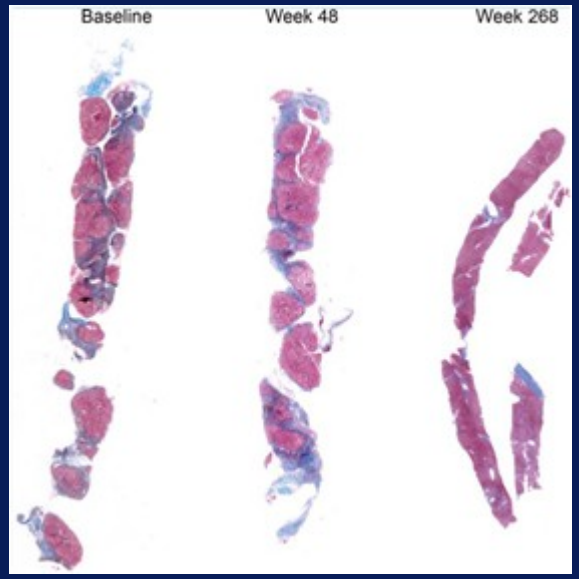
HCC incidence ≥ 1.5% per year in cirrhotics[1]

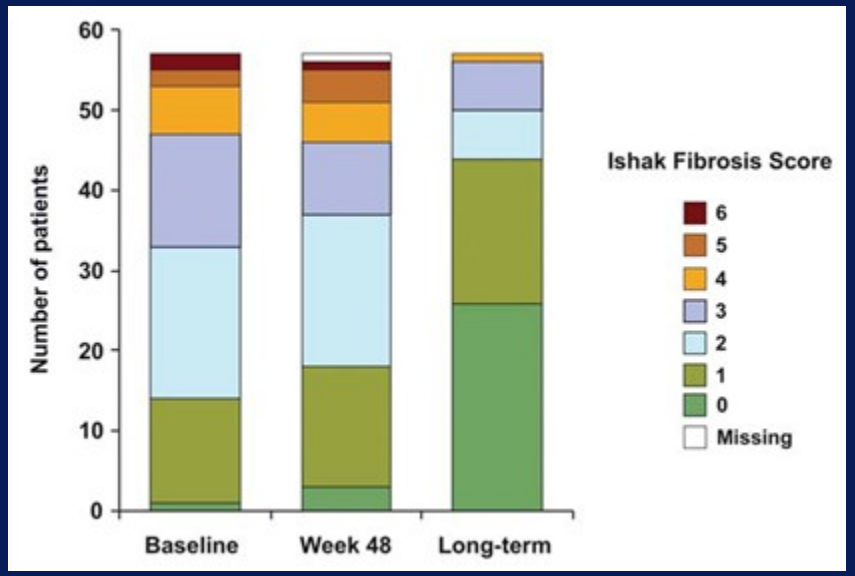
HCC incidence ≥ 0.2% per year in HBV carriers[2]

1. Sarrazin et al, Am J Med 1996; 2. Bruix & Sherman Hepatology 2011

Reversal of Fibrosis and Cirrhosis Following ETV Therapy. Phase III and Rollover Studies

57 patients with < 300 copies/ml HBV-DNA had long-term liver biopsy (3-7 years)
10 had Ishak S > 5. 4 patients had Ishak S reduced by 1 to 4 points





Chang et al, Hepatology 2010;52:886-893

HCC May Also Develop in Non Cirrhotic Patients with Chronic Viral Hepatitis

HBV, Reveal [1]	164 incident HCCs diagnosed during 11.4 yr of follow-up 41,779 person-years of follow-up 33 (20%) without cirrhosis
HCV, HALT C [2]	48 incident HCC diagnosed during 4.6 yr of follow-up 8 (17%) with S_2-S_4

[1]Chen et al JAMA 2006;295:65-73; [2]Lok et al Gastroenterology 2009;136:138-148;