The long term impact of NA treatment on the outcome of liver disease in CHB

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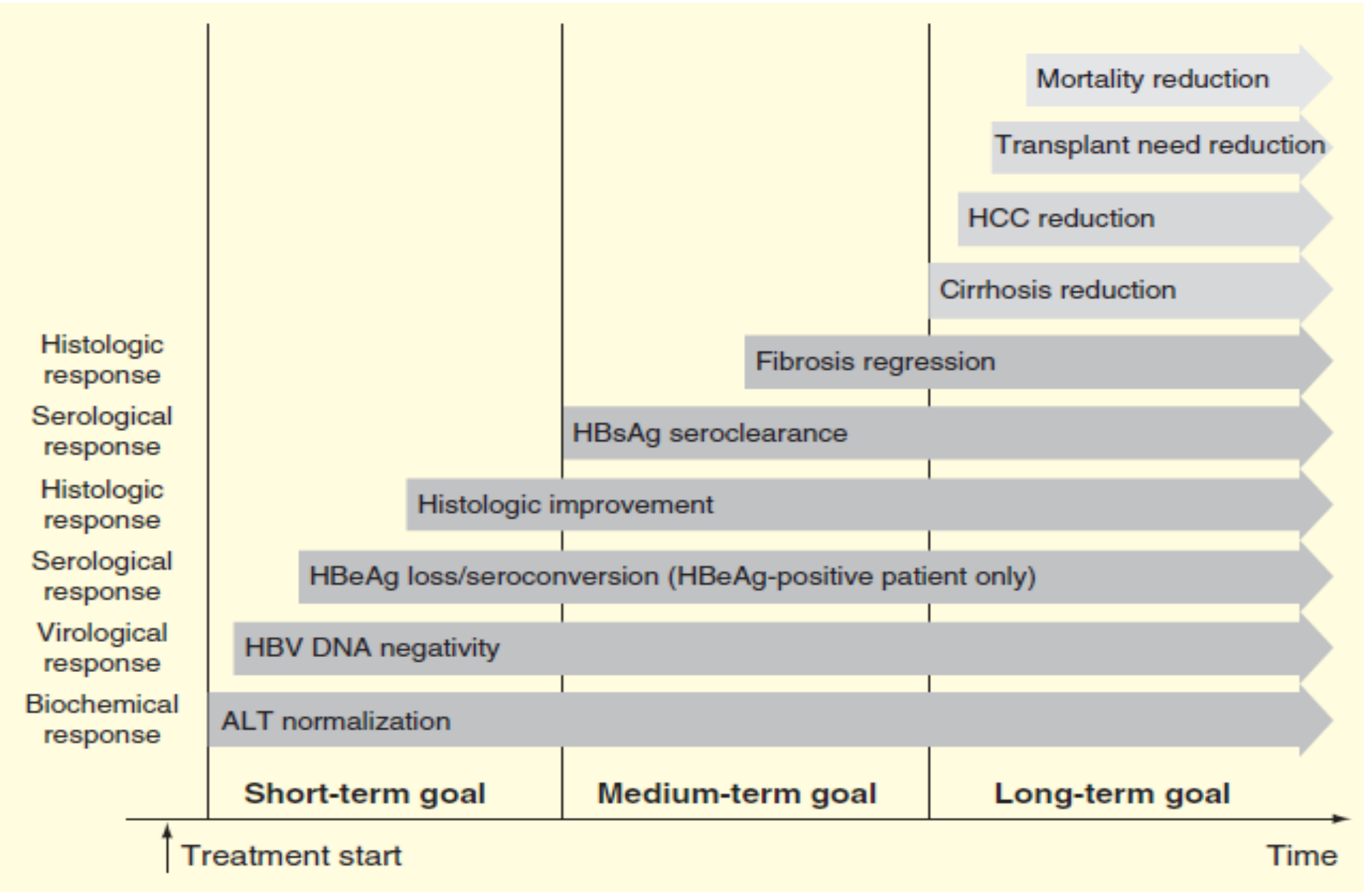
Outline

- Current treatment of CHB
- Impact of long-term NA therapy on HCC reduction in Asian CHB patients
  - Japan
  - Hong Kong
  - Korea
    - C-TEAM (Taiwan)
- Perspectives

Clinical goals of CHB therapy



Su and Kao. ERGH 2014.

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Treatment landscape of CHB: 2015

Generic Name	Trade Name	Manufacturer	Date Approved for Hepatitis B
Interferon alfa	INTRON® A ROFERON ®	Schering Hoffman La-Roche	1991
Lamivudine	ZEFFIX®	GlaxoSmithKline	1998
Adefovir dipivoxil	HEPSERA™	GlaxoSmithKline	2002
*Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
*Peginterferon alfa-2a	PEGASYS®	Hoffman La-Roche	2005
Telbivudine	SEBIVO™	Novartis	2006
*Tenofovir	VIREAD™	Gilead Sciences	2008

*Preferred agents

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High virological responses with long-term ETV or TDF

Response	ETV		TDF	
	HBeAg+ Patients Year 5[1]	HBeAg- Patients Year 3[2,a]	HBeAg+ Patients Year 7[3]	HBeAg- Patients Year 7[3]
HBV DNA suppression[b]	**94%** (88/94)	**95%** (54/57)	**99%** (159/160)	**99%** (271/273)
Resistance	**1% (n=1)**	NR	**0%**	**0%**
HBsAg loss (seroconversion)	**1.4%** (0%)	NR	**12% (10%)**	**<1% (<1)**

Not head to head trials

*Neither Truvada (TVD=TDF + FTC) nor emtricitabine (FTC) are licensed for use in CHB; [a]ETV re-treatment (relapsed <6 months post-treatment in ETV-027 study); [b]TDF: HBV DNA <400 copies/mL, ETV: HBV DNA <300 copies/mL; HBeAg: hepatitis B e antigen; NR: not reported; ETV: entecavir; TDF: tenofovir disoproxil fumarate

1. Chang TT et al. Hepatology 2010;51:422–30;
2. Shouval D et al. Hepatology 2008; Abstract 927;
3. Marcellin P et al. AASLD 2013 Abstract 926

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Table 2. The histologic improvement and fibrosis regression after prolonged nucleos(t)ide analog therapy.

Parameter	Lamivudine	Adefovir	Entecavir	Tenofovir
Treatment duration (year)	3	4–5	3–7	5
Patient number	63	45	57	348
HAI necroinflammatory score[†]				
Improvement	56%	83–86%	96%	87%
Progression	11%	NA	NA	NA
Bridging fibrosis[‡]				
Improvement	63%	73–75%	88%	51%
Progression	9%	NA	NA	NA
Advanced fibrosis/cirrhosis[‡]				
Improvement	73%	NA	100%	74%
Progression	2%	NA	NA	1%

[†]Histologic improvement is defined as ≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis.
[‡]The regression of fibrosis is defined as ≥1 unit decrease by Ishak scoring system.
HAI: Histology activity index; NA: Not available.

Su and Kao. ERGH 2014.

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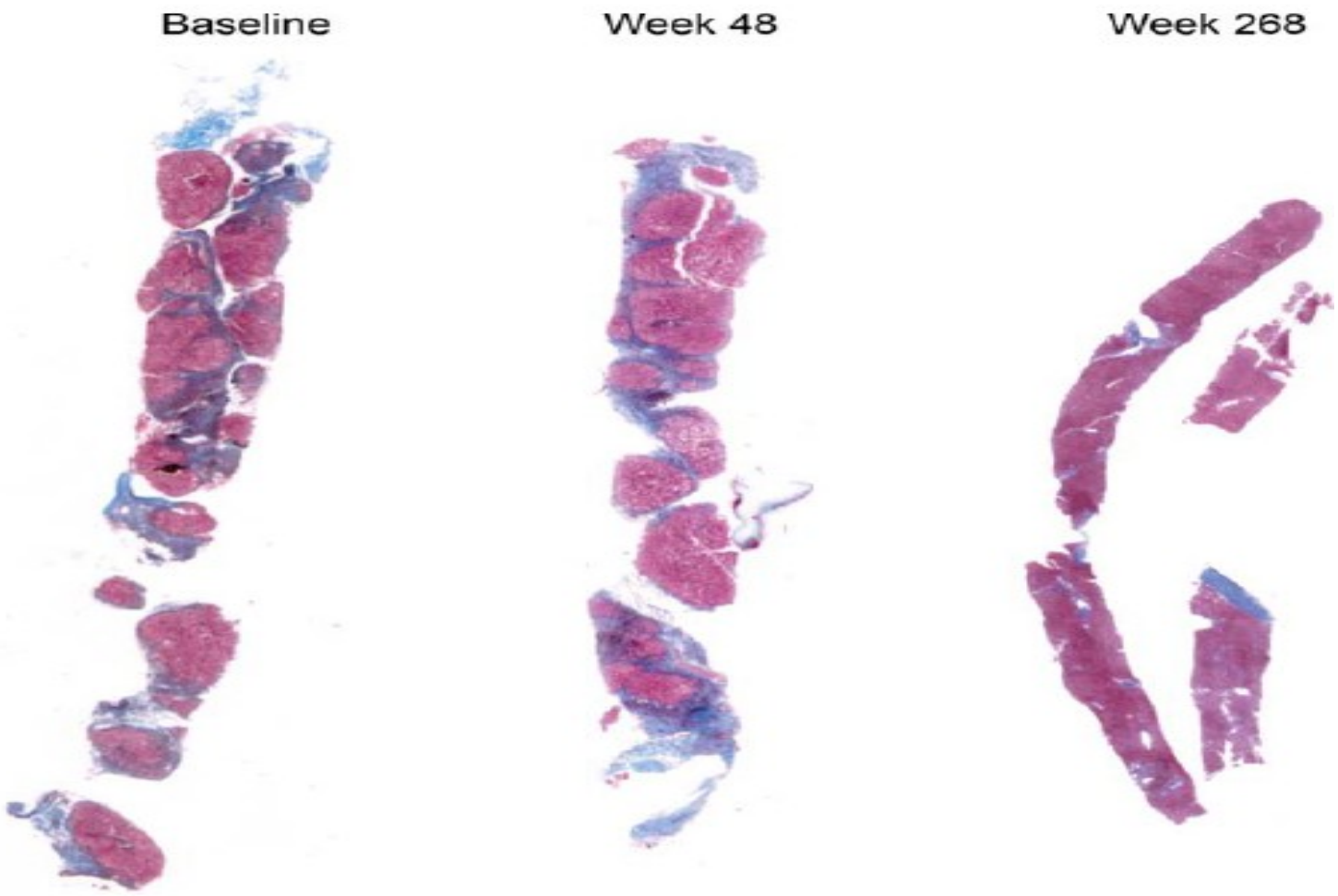
Entecavir-treated patient with serial liver biopsies



Chang TT et al. Hepatology 2010;52:886–893

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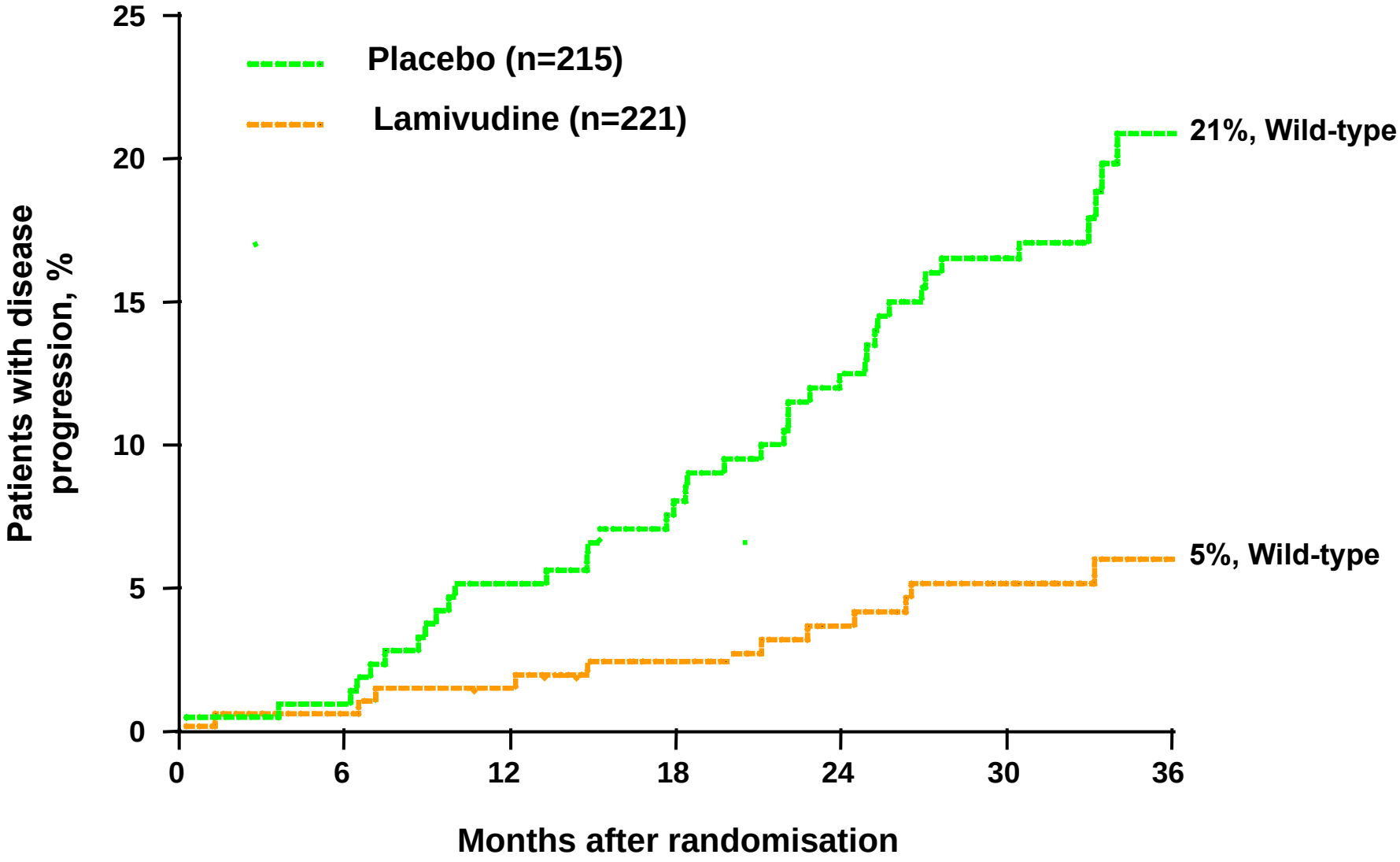
Antiviral agents delay disease progression



Adapted from Liaw Y-F. *Semin Liver Dis* 2005;25:40–47; Liaw Y-F, *et al. N Engl J Med* 2004;351:521–31.

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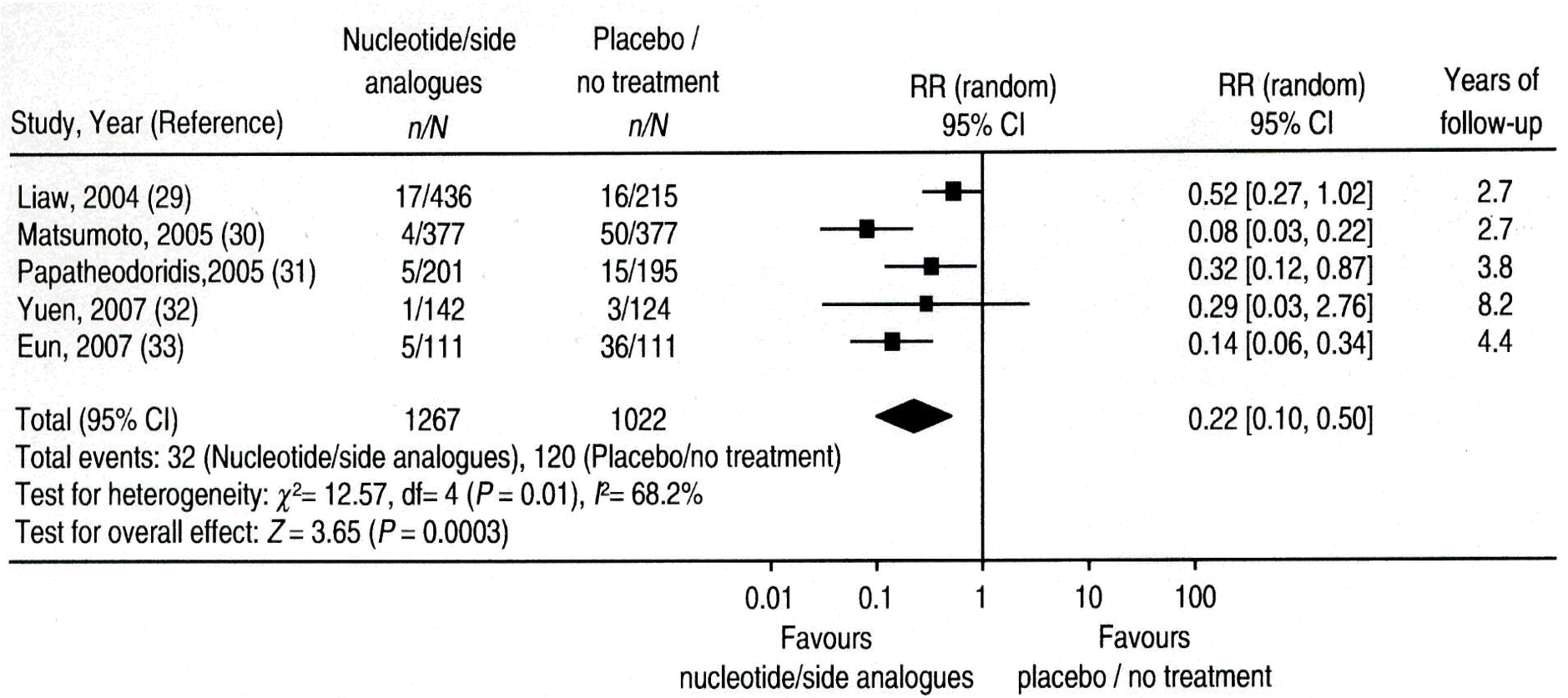
Pooled data from 5 studies showed about four-fold reduction of HCC in NA group (2.5%) against the control group (11.7%)



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

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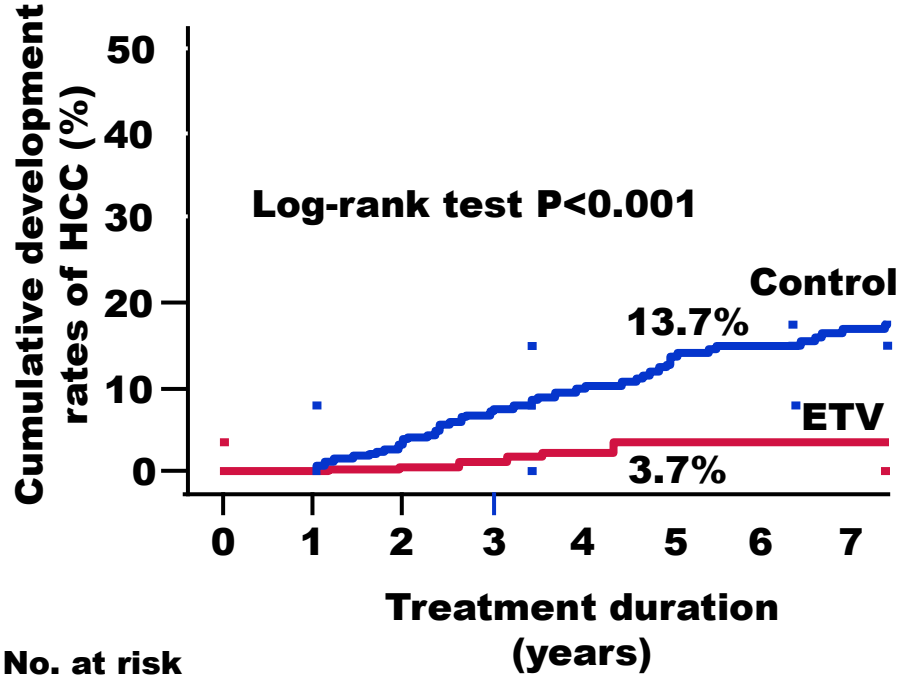
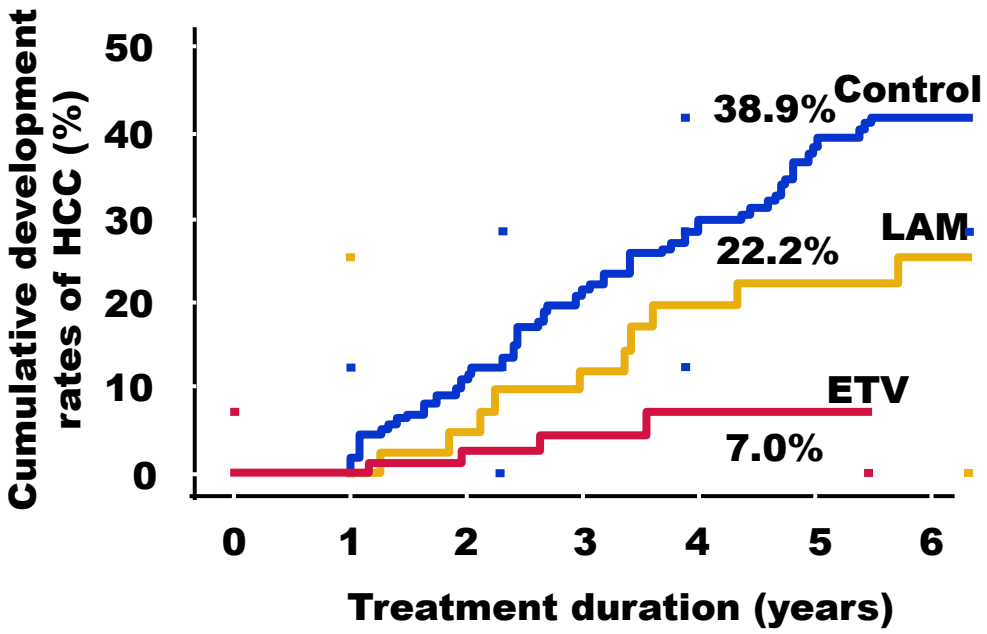
HCC incidence is lower in patients treated with ETV vs. control

All patients



No. at risk								
ETV	316	316	264	185	101	44	2	2
Control	316	316	277	246	232	200	187	170

Cirrhotics



No. at risk						
ETV	79	79	72	53	35	17
LAM	49	49	41	35	32	29
Control	85	85	76	65	64	47

Hosaka et al. Hepatology

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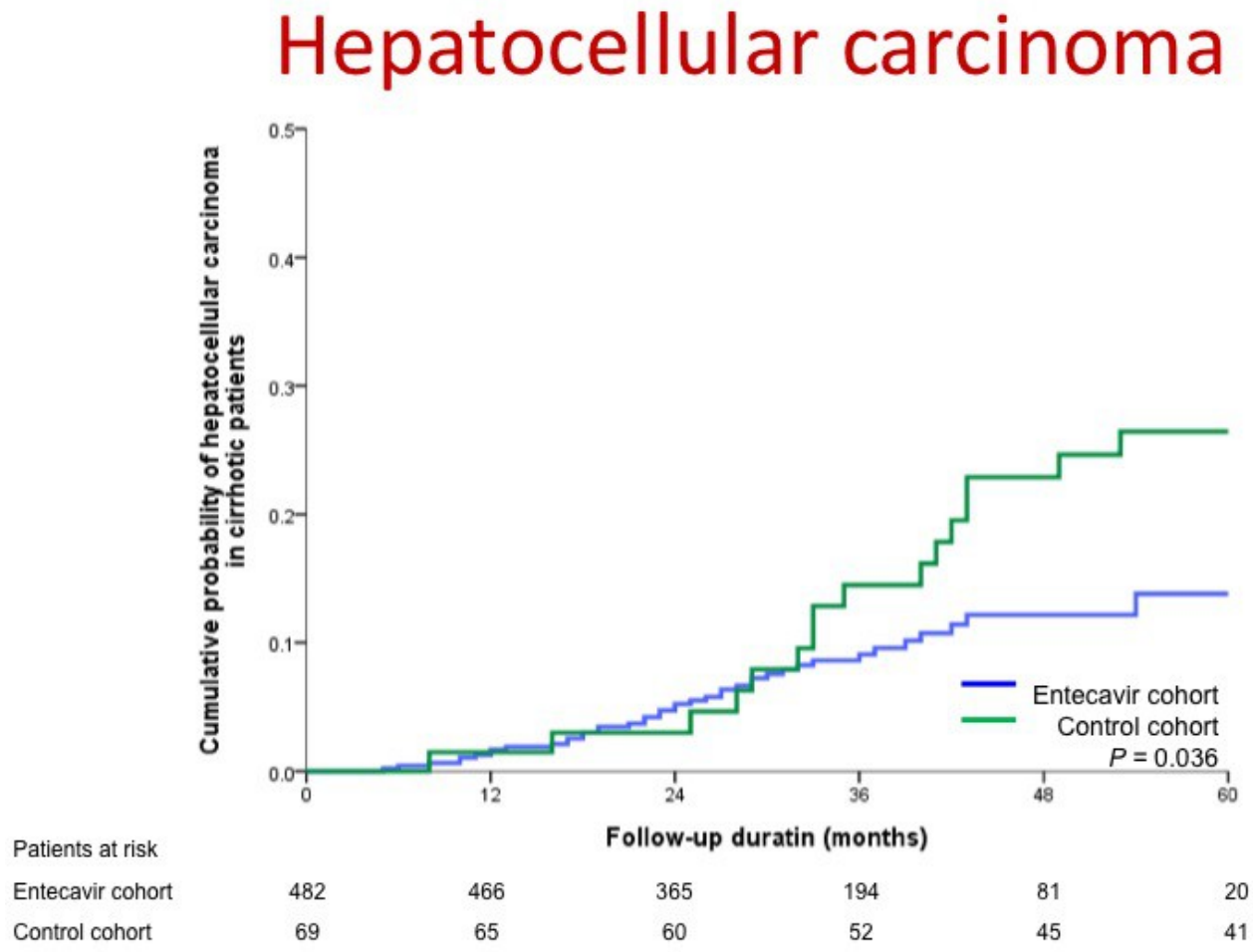
Entecavir therapy reduces clinic events in cirrhotic patients



Wong et al. Hepatology 2013.

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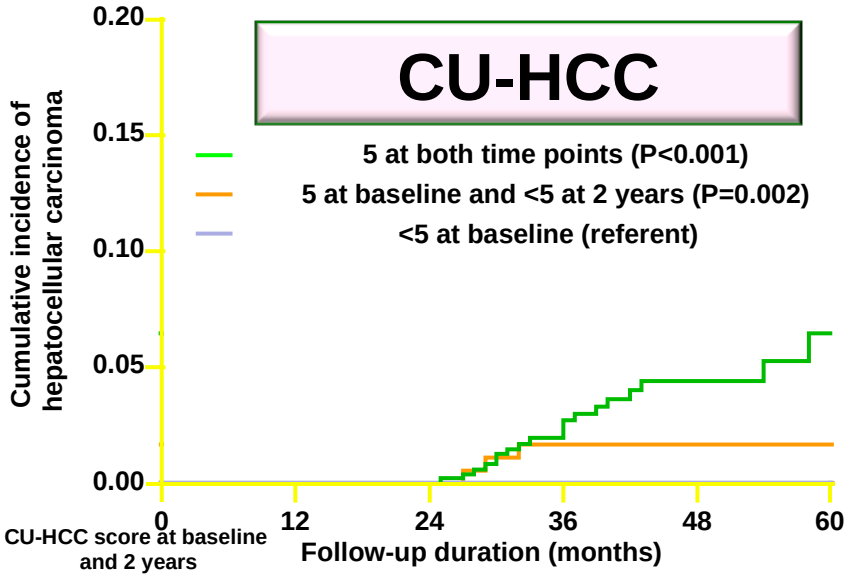
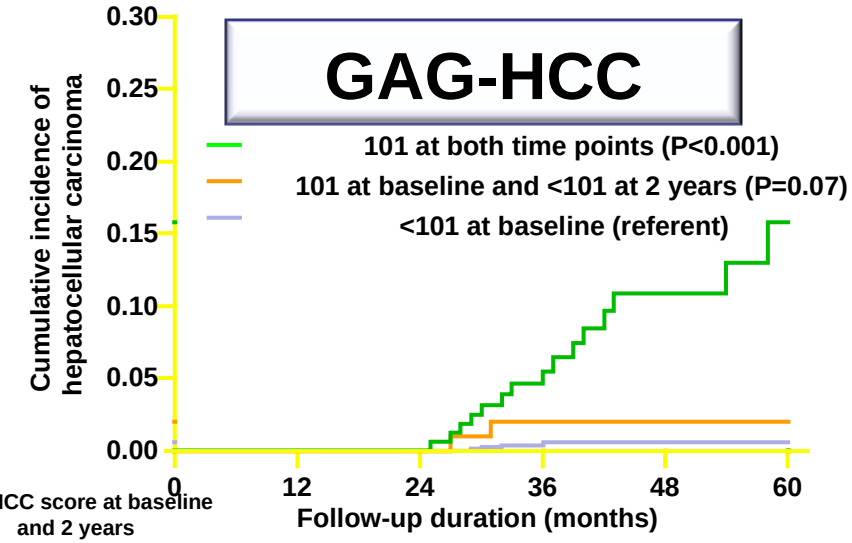
Changes in risk scores and HCC



CU-HCC score at baseline and 2 years

Patients under observation:

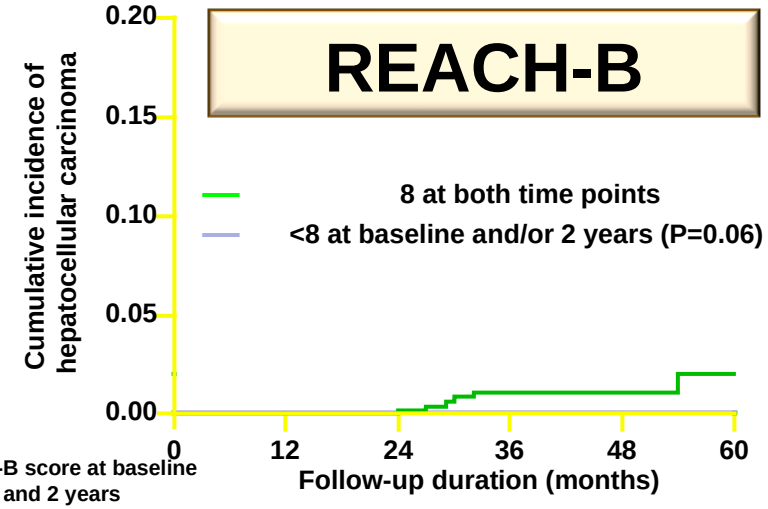
5 at both	540	540	520	379	180	63
5 and <5	197	197	187	147	78	43
<5 at baseline	673	673	645	529	262	61



GAG-HCC score at baseline and 2 years

Patients under observation:

101 at both	187	187	183	113	58	25
101 and <101	115	115	114	75	38	13
<101 at baseline	1108	1108	1106	843	391	150



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	115

Wong et al. Gastroenterology 2013.

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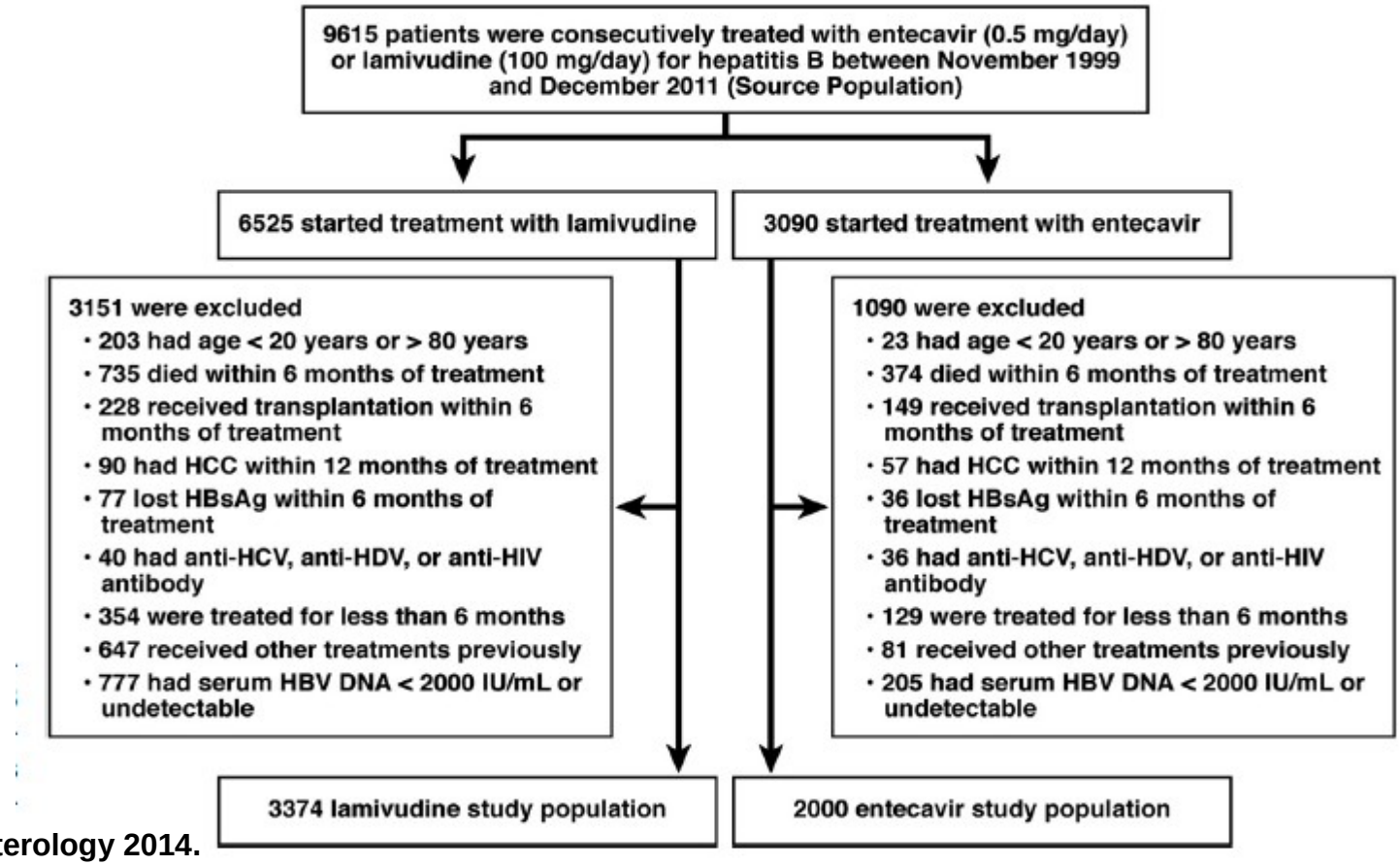
Mortality, Liver Transplantation, and Hepatocellular Carcinoma Among Patients With Chronic Hepatitis B Treated With Entecavir vs Lamivudine

Young–Suk Lim,[1] Seungbong Han,[2] Nae–Yun Heo,[3] Ju Hyun Shim,[1] Han Chu Lee,[1] and Dong Jin Suh[1]

[1]Department of Gastroenterology, Liver Center, [2]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea; [3]Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea



Lim et al. Gastroenterology 2014.

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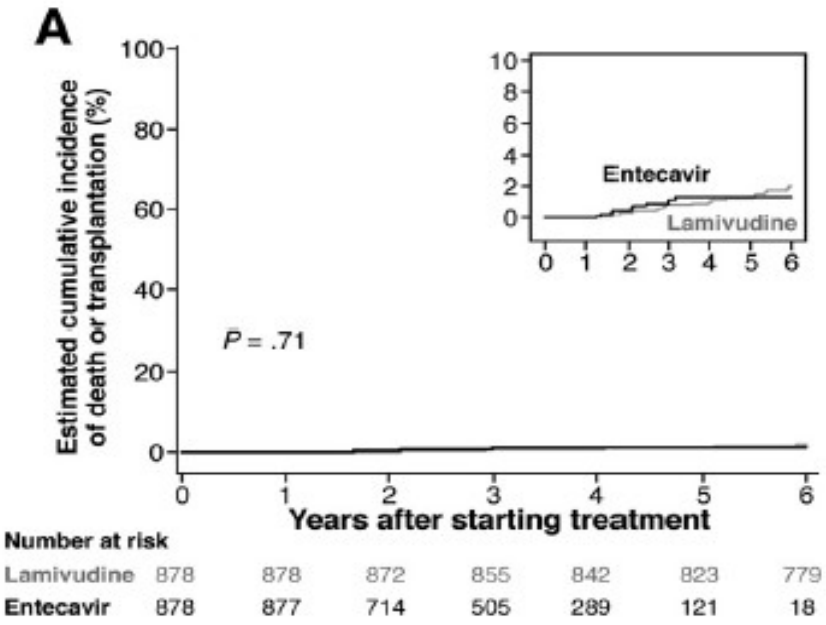
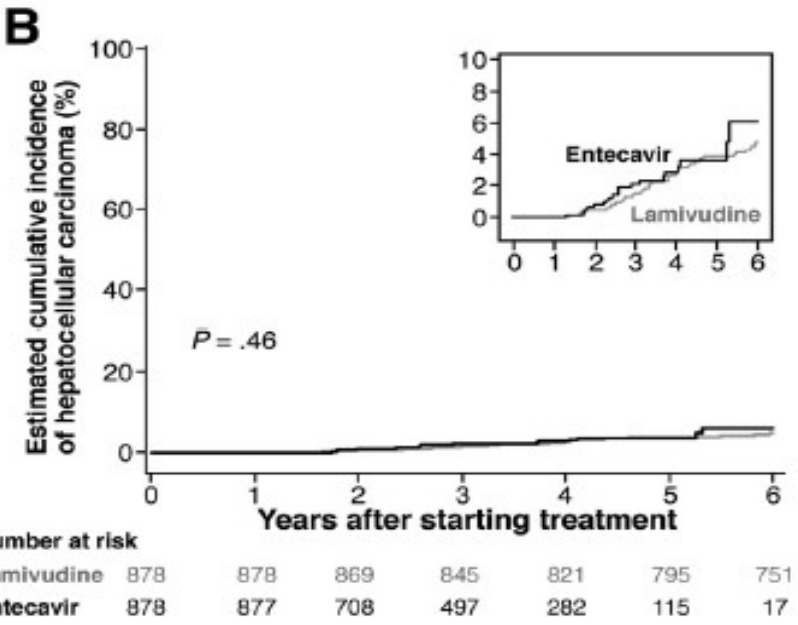
NC





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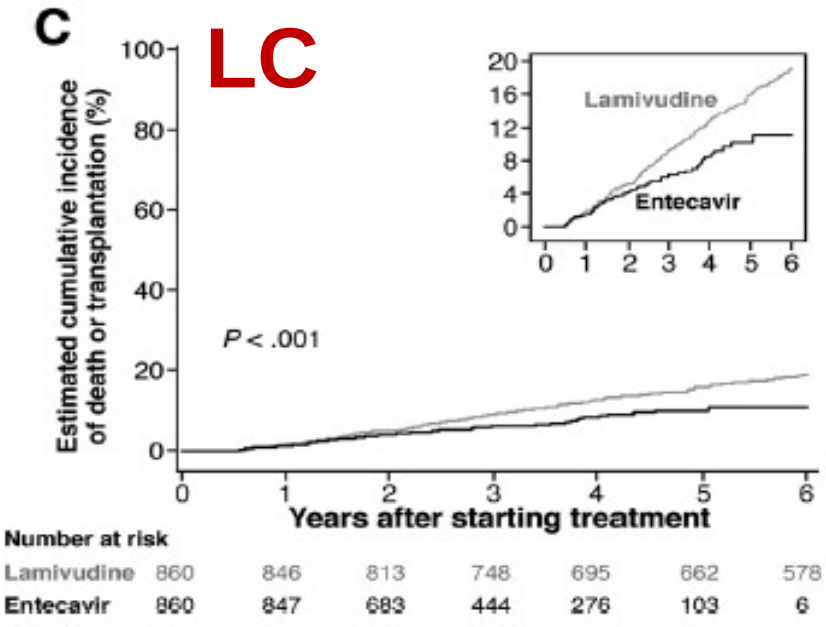

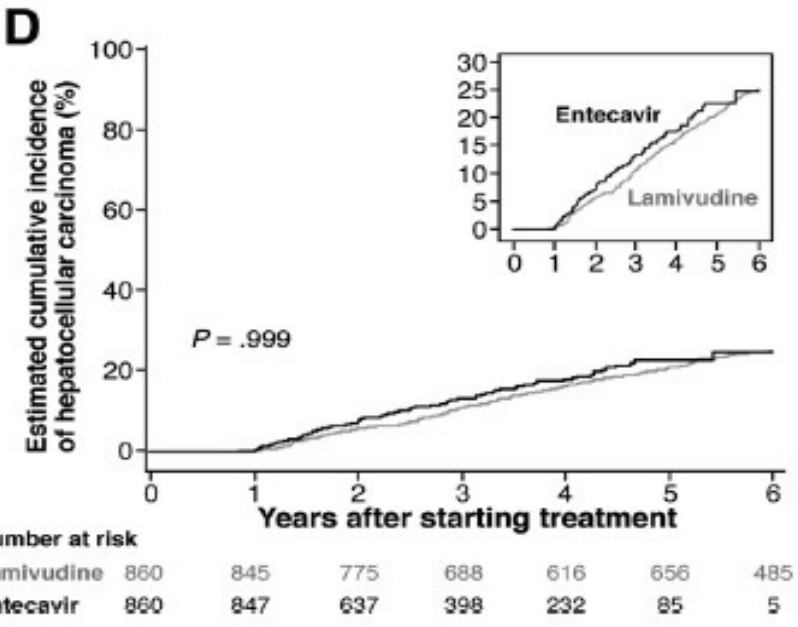

Lim et al. Gastroenterology 2014.

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Reduction of hepatocellular carcinoma in hepatitis B-related cirrhosis patients with long-term entecavir therapy - A follow-up report of C-TEAM study

Tung-Hung Su, Tsung-Hui Hu, Chi-Yi Chen, Yi-Hsiang Huang, Wan-Long Chuang, Chun-Che Lin, Chia-Chi Wang, Wei-Wen Su, Cheng-Yuan Peng, Rong-Nan Chien, Lein-Ray Mo, Yi-Wen Huang, Ming-Yao Chen, Chih-Lin Lin, Tsung-Ming Chen, Horng-Yuan Wang, Kuo-Chih Tseng, Sheng-Shun Yang, Shih-Jer Hsu, Fat-Moon Suk, Chi-Tan Hu, Tsai-Yuan Hsieh, Ming-Jong Bair, Cheng-Chao Liang, Tai-Chung Tseng, Chi-Ling Chen, Jia-Horng Kao on behalf of the C-TEAM study group, TAIWAN

Su and Kao et al. AASLD 2013; oral #189

Su and Kao et al. AASLD 2014; LB-30

Study design (I)

- Multi-center, observational, cohort study with long-term FU to evaluate the prognosis of ETV-treated HBV-related cirrhosis patients
- Primary endpoint
  - HCC reduction
- Secondary endpoint: reduction in the incidence rates of
  - EV/GV bleeding
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Ascites
  - Liver-related mortality

Su and Kao et al. AASLD 2013; oral #189

Study Design (II)

- **Inclusion criteria of Treatment group**
  - **HBsAg (+) > 6 months, anti-HCV (-)**
  - **Baseline serum HBV DNA ≧ 2000 IU/mL**
  - **Child A cirrhosis**
    - **Liver biopsy （Metavir F4 or Ishak > 5) or**
    - **Ultrasonographic evidence of cirrhosis with signs of portal hypertension (splenomegaly or presence of EV/GV)**
  - **Treatment naïve**
  - **No HCC development within the first year**
  - **Long-term ETV monotherapy**
- **Historical control group: Untreated compensated cirrhotic controls collected from 1985-1995**

Su and Kao et al. AASLD 2013; oral #189

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Cirrhosis Taiwanese EntecAvir Multicenter Study

Chung-Shan Med Univ Hosp
Changhua Christian Hosp
China Med Univ Hosp
Tungs' MetroHarbor Hosp
Taichung Vet Gen Hosp

Natl Taiwan Univ Hosp
Taipei Vet Gen Hosp
Tzu-Chi Gen Hosp, Taipei
Chang-Gung Mem Hosp, Keelong
McKay Mem Hosp, Taipei
Cathy Gen Hosp
Shuang-Ho Hosp
Taipei City Hosp, Ren-Ai
Wan Fang Hosp
Tri-service Gen Hosp
Far Eastern Mem Hosp

Chia-Yi Christ Hosp
Tzu-Chi Gen Hosp, Chiyi
Natl Taiwan Univ Hosp, YL

Tzu-Chi Gen Hosp, Hualien
McKay Mem Hosp, Taitung

Chang-Gung Mem Hosp, Kaohsiung
Kaohsiung Med Univ Hosp
E-Da Hosp

24 academic centers in Taiwan

Su and Kao et al. AASLD 2014; LB-30

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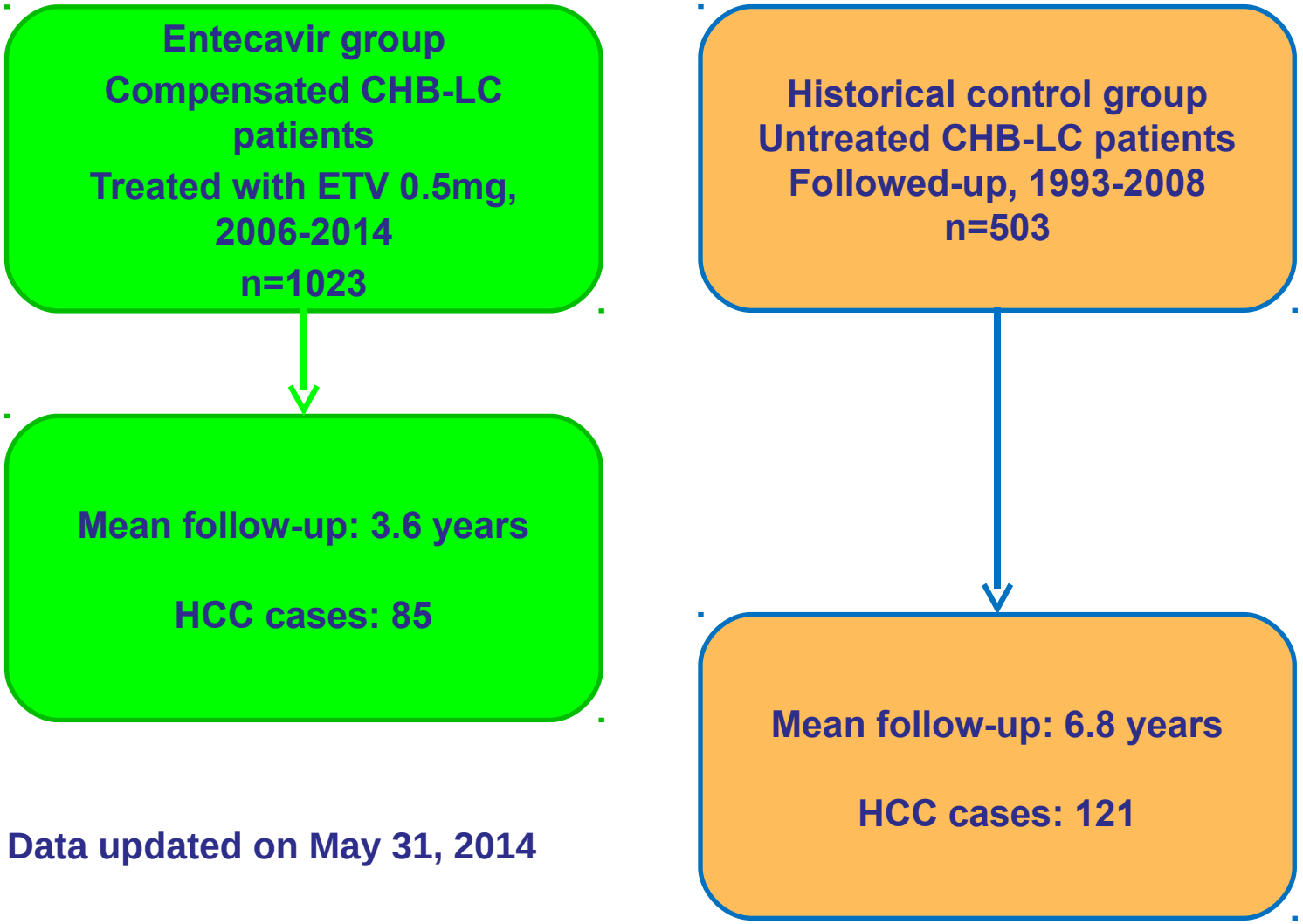
Results- Patients enrolment



Data updated on May 31, 2014

Su and Kao et al. AASLD 2014; LB-30

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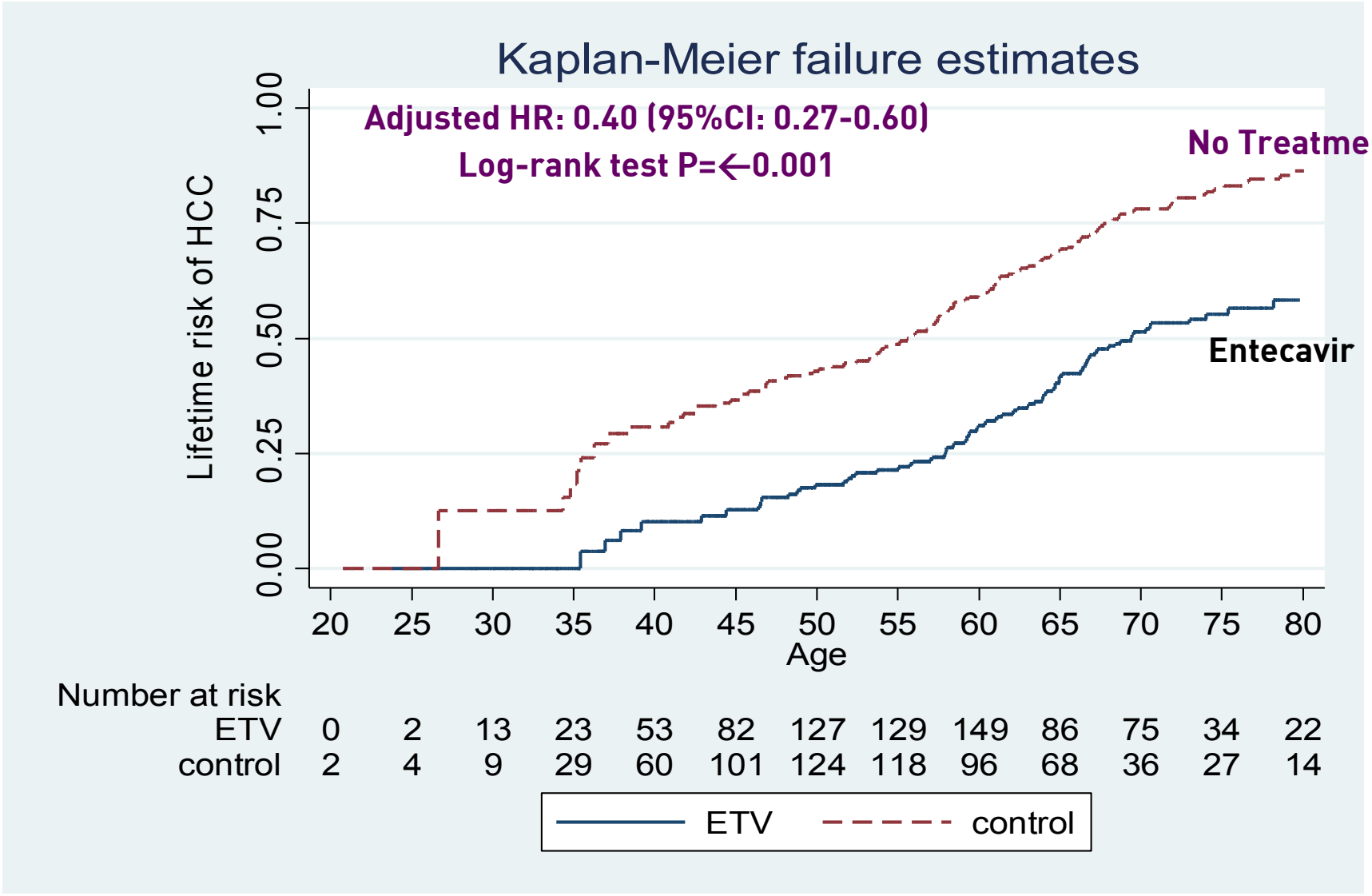
Baseline characteristics of patients in ETV treatment and untreated control groups

	ETV	Control	P
n	1123	503	
Age, year	54.8(11.3)	50.5(11.8)	<.001
Male	826 (74)	385 (77)	0.202
ALT, U/L	115(222)	59(60)	<.001
Albumin, g/dL	3.9(0.6)	4.2(0.4)	<.001
T-bil, mg/dL	1.4(2.0)	1.0(0.5)	<.001
Platelet, K/uL	122(52)	141(53)	<.001
HBeAg-negative	795	354	0.576
HBV DNA, log IU/mL	5.6(1.3)	5.5(1.3)	0.325
AFP, ng/mL	23(85)	48(348)	0.159
Prior cirrhotic complications			
EV/GV bleeding	37 (3)	14 (3)	0.584
Spontaneous bacterial peritonitis	2	0	0.344
Hepatic encephalopathy	2	1	0.928
Liver decompensation	4	0	0.180
Follow-up duration, year	3.6(1.3)	6.8(4.5)	<.001

Su and Kao et al. AASLD 2014; LB-30

The lifetime incidence of HCC development between entecavir and no-treatment group



Su and Kao et al. AASLD 2014; LB-30

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Multivariate analysis to predict HCC
by Cox regression model

Parameters	Hazard ratio	95% CI	P value
Age (1 year increment)	1.04	0.99-1.09	.151
Male (vs. female)	1.89	1.24-2.88	.003
Entecavir treatment (vs. no treatment)	0.40	0.27-0.60	<.001
ALT (1 U/L increment)	1.00	1.00-1.00	.221
T-bil (1 mg/dL increment)	1.04	0.92-1.17	.513
PLT (1 k/uL increment)	0.996	0.99-0.9996	.030
Albumin (1 g/L increment)	0.61	0.43-0.87	.006
AFP (1 ng/mL increment)	1.00	1.00-1.00	.855
HBeAg positive (vs. negative)	1.38	0.94-2.03	.099
HBV DNA (1 log IU/mL increment)	1.02	0.89-1.16	.800

Entecavir treatment was associated with 60% reduction of HCC risk (adjusted hazard ratio: 0.40, 95% CI: 0.27-0.60) in cirrhosis patients

Su and Kao et al. AASLD 2014; LB-30

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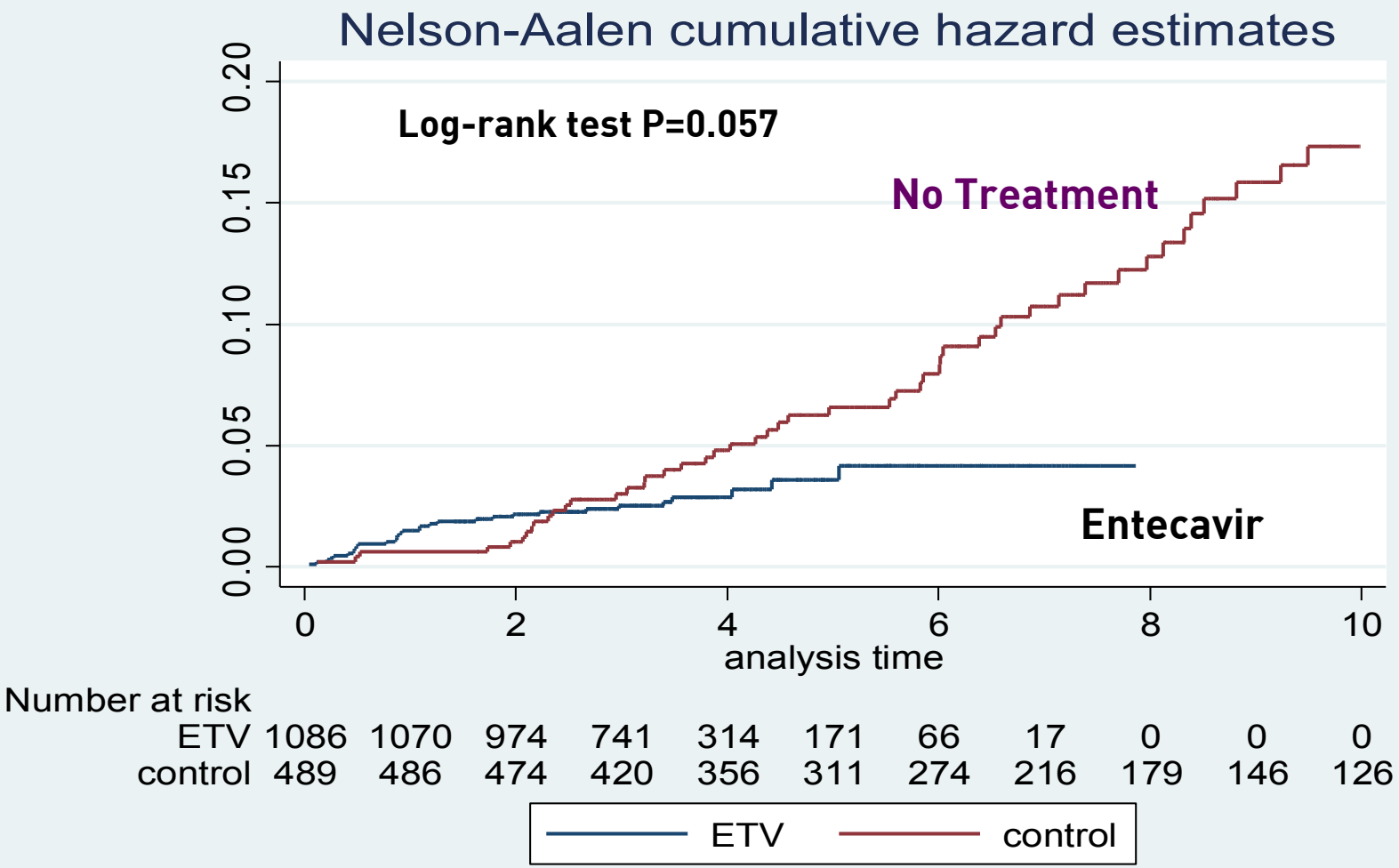
The effects of entecavir on cirrhotic complications

- **Variceal bleeding**



Su and Kao et al. AASLD 2014; LB-30

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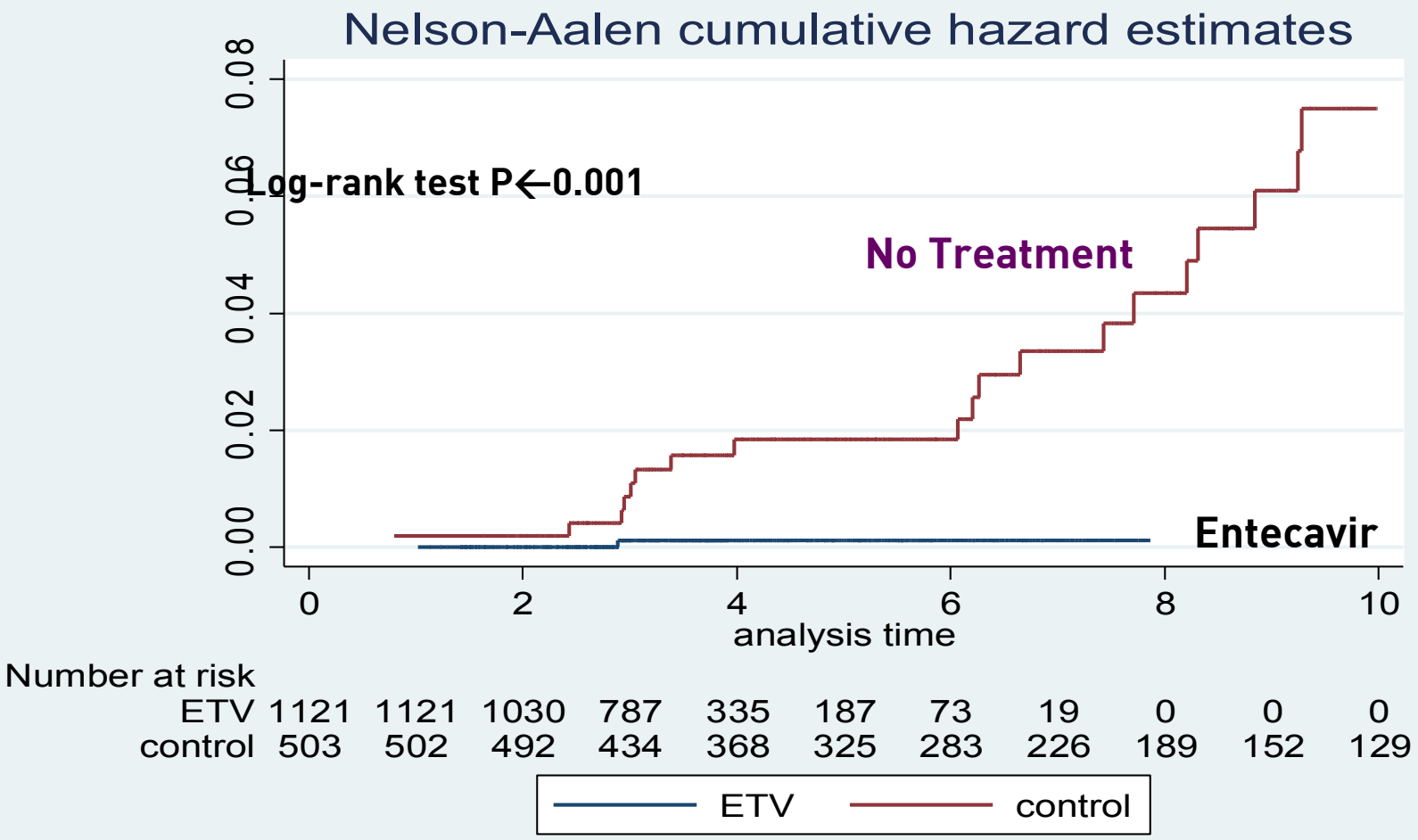
The effects of entecavir on cirrhotic complications

- **Spontaneous bacterial peritonitis**



Su and Kao et al. AASLD 2014; LB-30

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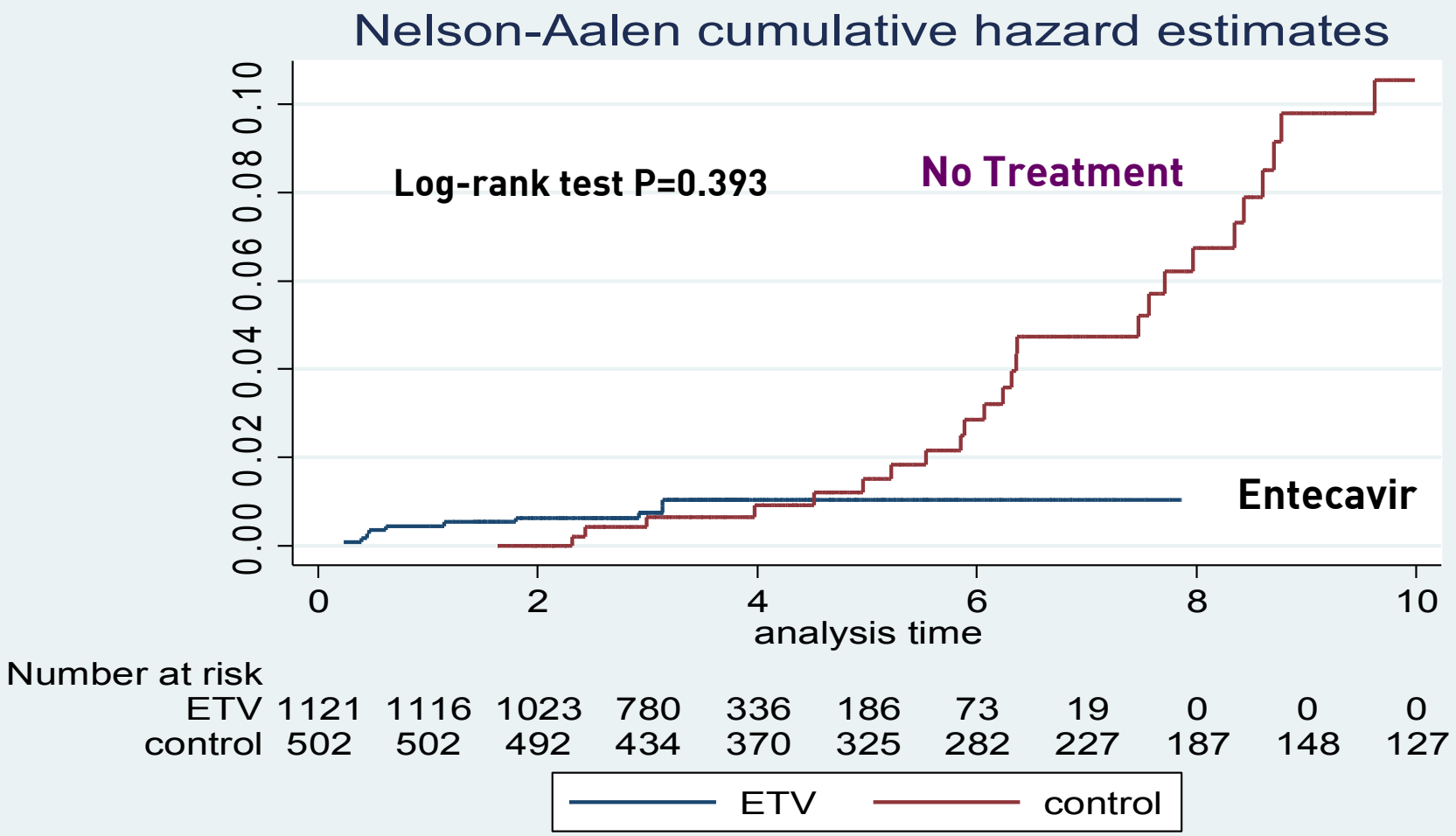
The effects of entecavir on cirrhotic complications

- **Hepatic encephalopathy**



Su and Kao et al. AASLD 2014; LB-30

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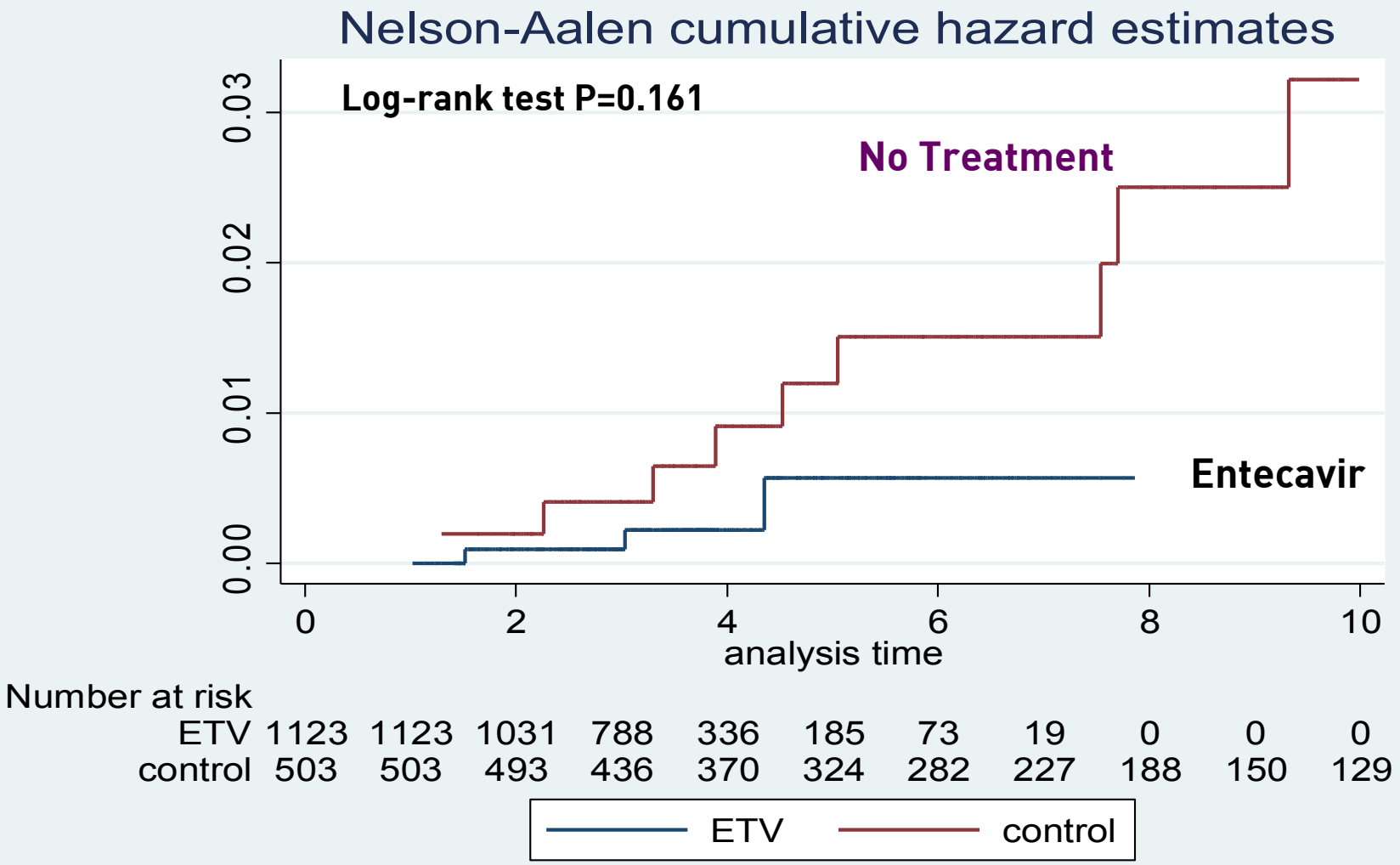
The effects of entecavir on liver transplantation



Su and Kao et al. AASLD 2014; LB-30

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Summary

- In this large cohort study, long-term entecavir therapy significantly reduced the development of HCC and spontaneous bacterial peritonitis in hepatitis B-related cirrhosis patients

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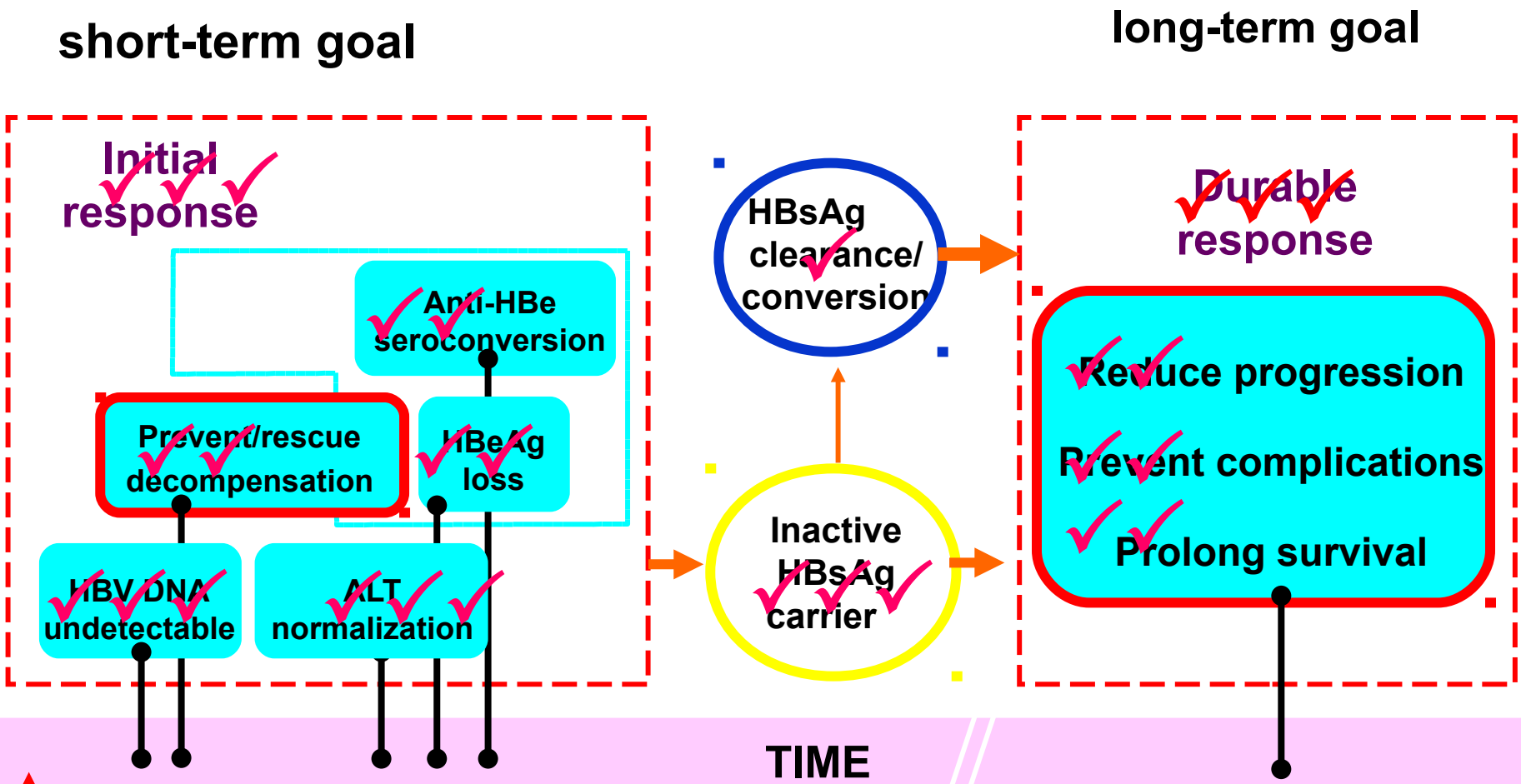
Goals of therapy for chronic HBV infection



✓ Goals achievable but not satisfactory!!

→ We need novel agents to cure HBV

Courtesy of Prof. YF Liaw

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Table 4. Developing therapeutic agents against hepatitis B virus infection.

Drug name	Mechanism of action	Clinical trial status
Nucleoside analog		
Emtricitabine	DNA polymerase inhibition	Should combine with other antiviral agents
Nucleotide analog prodrug		
Besifovir	DNA polymerase inhibition	Phase III, NCT01937806 [119]
Tenofovir alafenamide fumarate	DNA polymerase inhibition	Phase III, NCT01940471 NCT01940341 [116,117]
Non-nucleos(t)ide analog		
Myrcludex-B	Viral entry inhibitor	Phase II
Bay 41-4109	Inhibits viral core formation	Phase I
REP 9AC	Blocks HBsAg release	Phase II
NVR-1221	Capsid inhibitor	Phase Ia
Immunomodulator		
GS-9620	TLR-7 agonist	Phase II, NCT02166047 [120]
Other		
ARC-520	RNA interference	Phase II, NCT02065336 [121]

Su and Kao. ERGH 2014

Kao 2015

OPEN

Emerging Microbes and Infections (2014) 3, e64; doi:10.1038/emi.2014.64

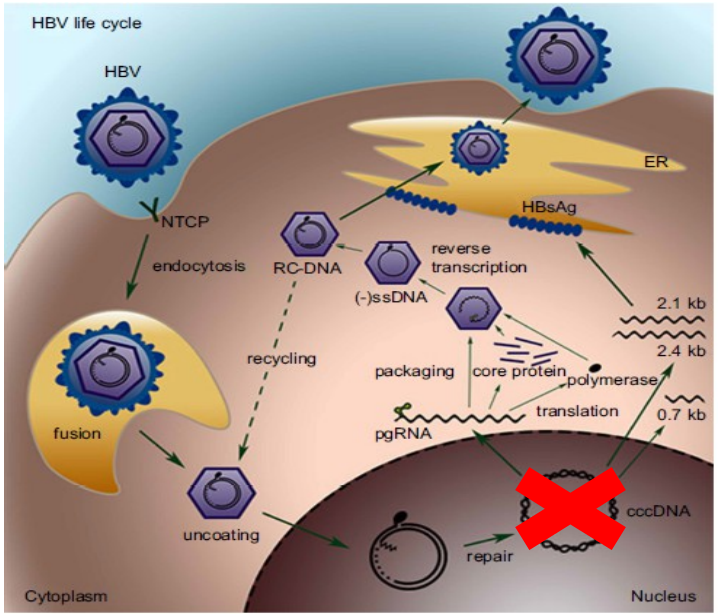
www.nature.com/emi

REVIEW

Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance

Hung-Chih Yang[1,2,3] and Jia-Horng Kao[2,3,4,5]

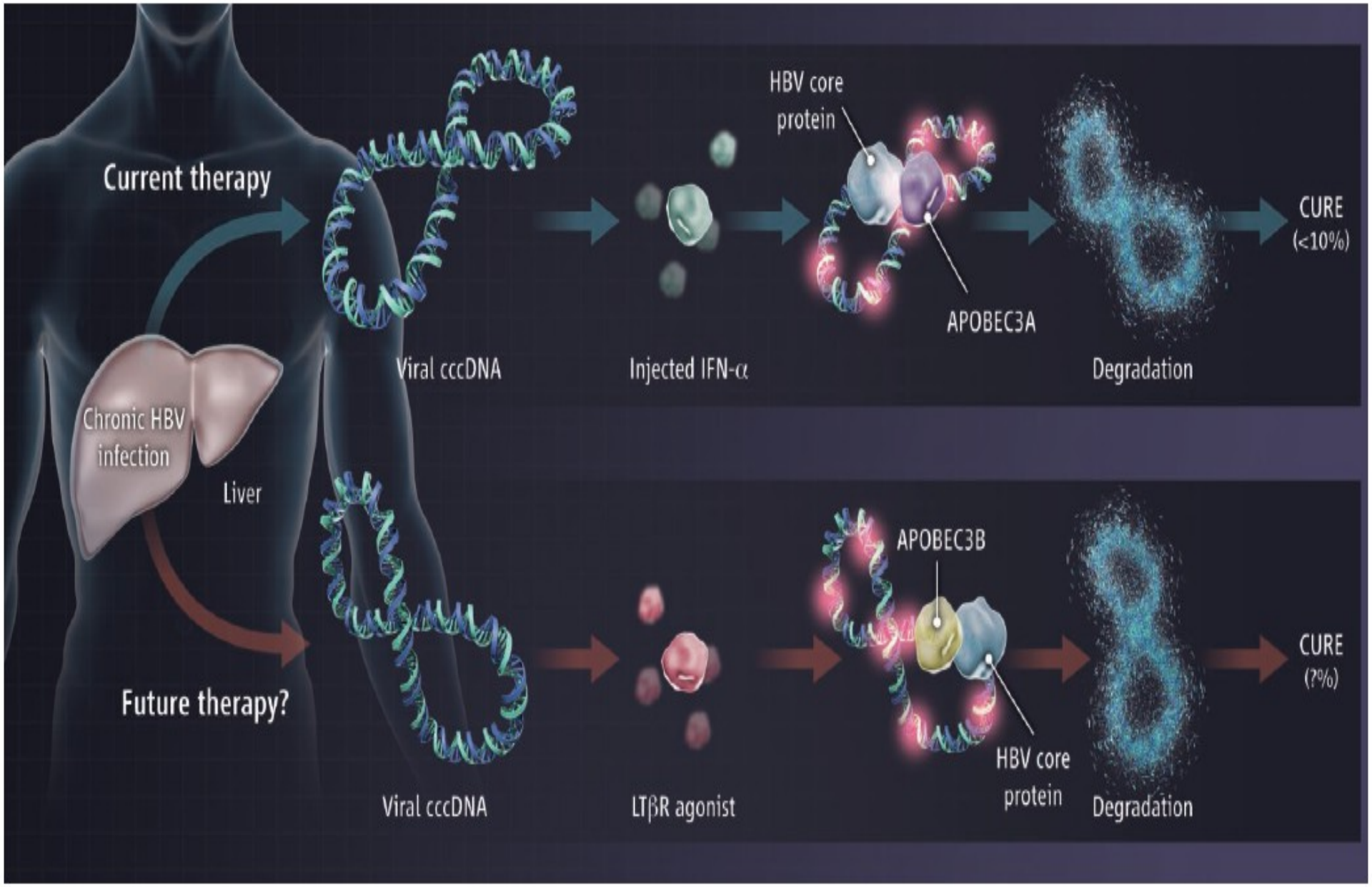
Covalently closed circular DNA (cccDNA) is the transcriptional template of hepatitis B virus (HBV). Extensive research over the past decades has unveiled the important role of cccDNA in the natural history and antiviral treatment of chronic HBV infection. cccDNA can persist in patients recovering from acute HBV infection for decades. This explains why HBV reactivation occasionally occurs in patients with resolved hepatitis B receiving intensive immunosuppressive agents. In addition, although advances in antiviral treatment dramatically improve the adverse outcomes of chronic hepatitis B (CHB), accumulating evidence demonstrates that current antiviral treatments alone, be they nucleos(t)ide analogs (NAs) or interferon (IFN), fail to cure most CHB patients because of the persistent cccDNA. NA suppresses HBV replication by directly inhibiting viral polymerase, while IFN enhances host immunity against HBV infection. Viral rebound often occurs after discontinuation of antiviral treatment. The loss of cccDNA can be induced by non-cytolytic destruction of cccDNA or immune-mediated killing of infected hepatocytes. It is known that NA has no direct effect on viral transcription or cccDNA stability. Therefore, the long half-life of hepatocytes leads to a very slow decline in cccDNA in patients under antiviral therapy. Novel antiviral agents targeting cccDNA or cccDNA-containing hepatocytes are thus required for curing chronic HBV infection.
Emerging Microbes and Infections (2014) **3**, e64; doi:10.1038/emi.2014.64; published online 17 September 2014



Yang and Kao. EMI (in press)

Kao 2015

IFN and cccDNA degradation



Science 2014;343:1212.

Kao 2015