National University Health System

Yong Loo Lin School of Medicine • National University Hospital • Faculty of Dentistry

National University Hospital

NUS National University of Singapore

Who to Treat? A critical review of International Guidelines

PHC, Jan 13-14, 2020

Prof Seng Gee Lim
Director of Hepatology,
Dept of Gastroenterology and Hepatology
National University Health System
Singapore

Disclosures

- Advisory Board
  - Gilead
  - Roche
  - Abbvie
  - Abbott
  - Springbank
  - Kaleido Bioscience
  - Romark Pharma
  - Arbutus
- Speaker’s Bureau
  - MSD
  - Gilead
  - Abbvie
  - Abbott

SINGAPORE HEPATOLOGY CONFERENCE

SHC

5 – 6 June 2020 • Singapore

Sharp focused updates in Hepatology

Welcome to Singapore!

www.shc-sg.com

THE SCIENCE OF HBV CURE

5 – 6 JUNE 2020 • Suntec Singapore

Presented by:

Singapore Hepatology Conference
7 - 8 June 2019 • Singapore

Agency for Science, Technology and Research

Endorsed by:

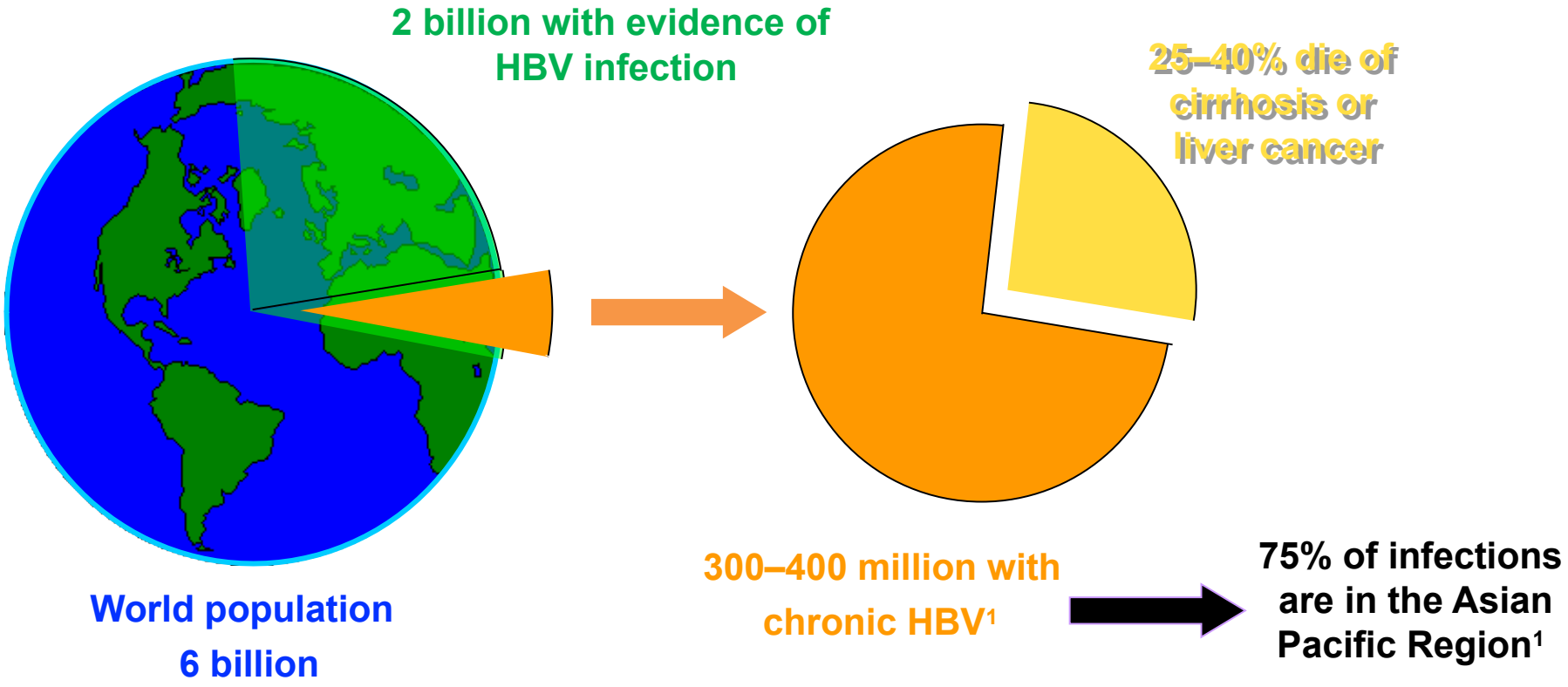
NUS National University of Singapore

ICE-HBV International Coalition to Eliminate HBV

www.scienceofhbvcure.com

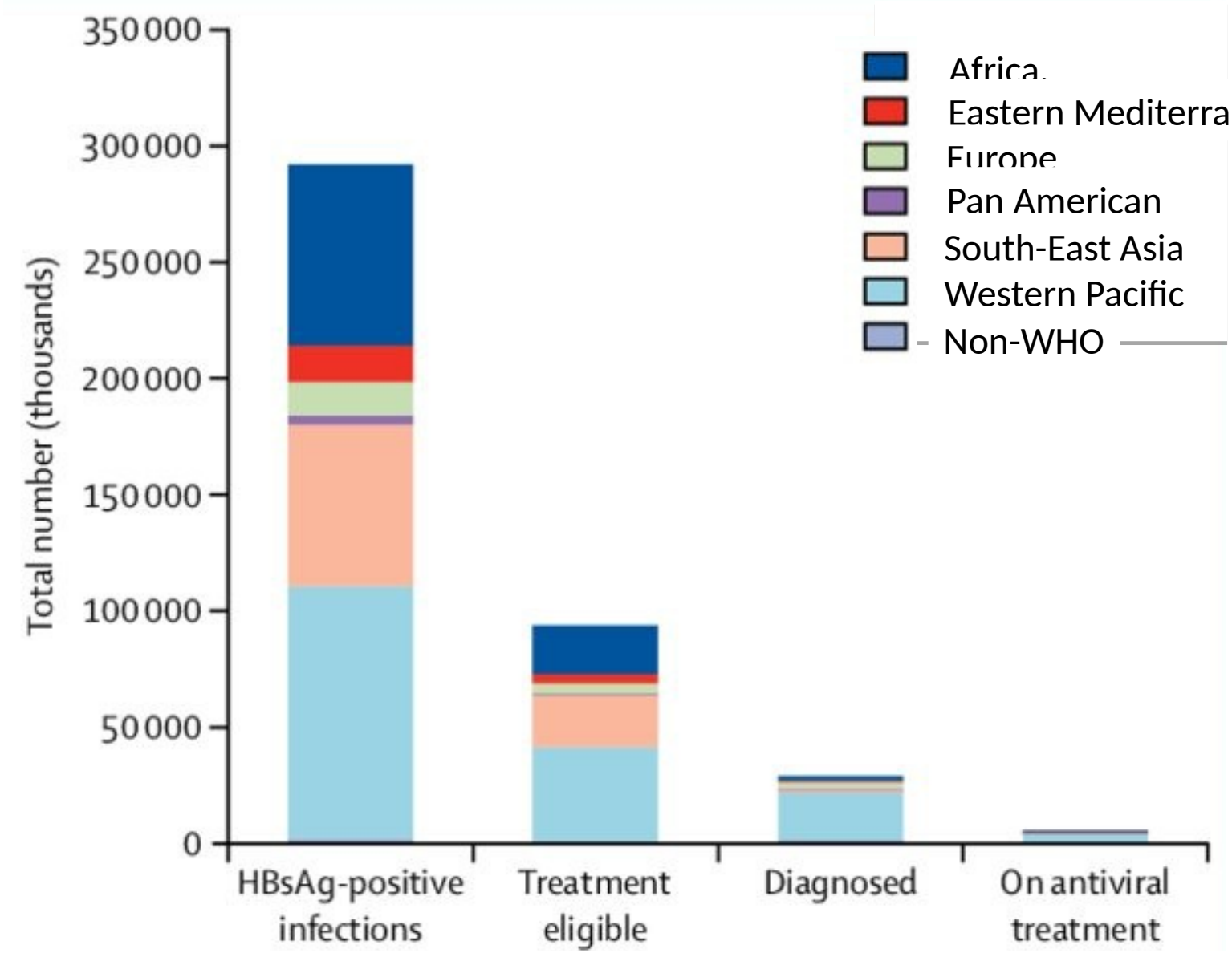
Global Impact of Chronic Hepatitis B

- Due to its high incidence and risk of Liver injury, CHB constitutes a significant health and economic burden within this region[2]



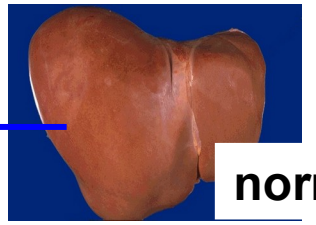
1. WHO and CDC fact sheets, available at www.who.int and www.cdc.gov
2. Rosmawati *et al*. *J. Gastroenterol. Hepatol.* 2004; **19**:958–969

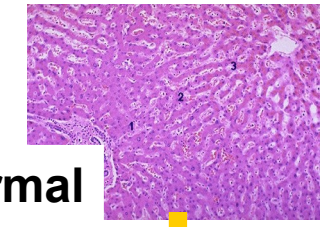
Burden of CHB by WHO region



Polaris Observatory Collaborators, Lancet Gastroenterol Hepatol.2018 Jun;3(6):383-403

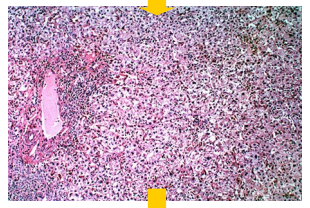
Natural History of HBV Infection





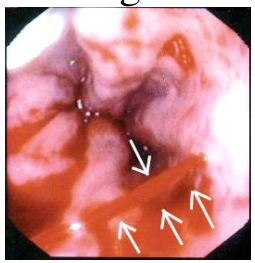
normal

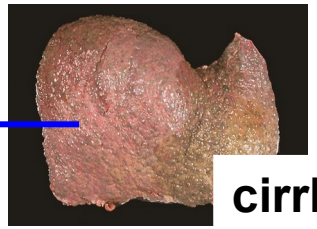
Immunotolerant

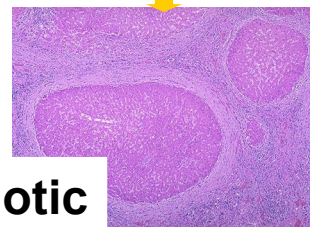


Chronic Hepatitis

Bleeding varices





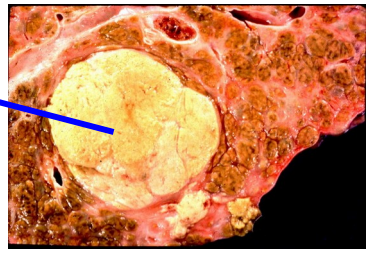


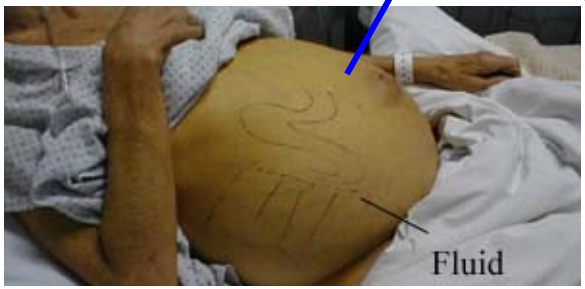
cirrhotic

Cirrhosis 18-20%

Decompensation 20-30%

HCC 6-15%



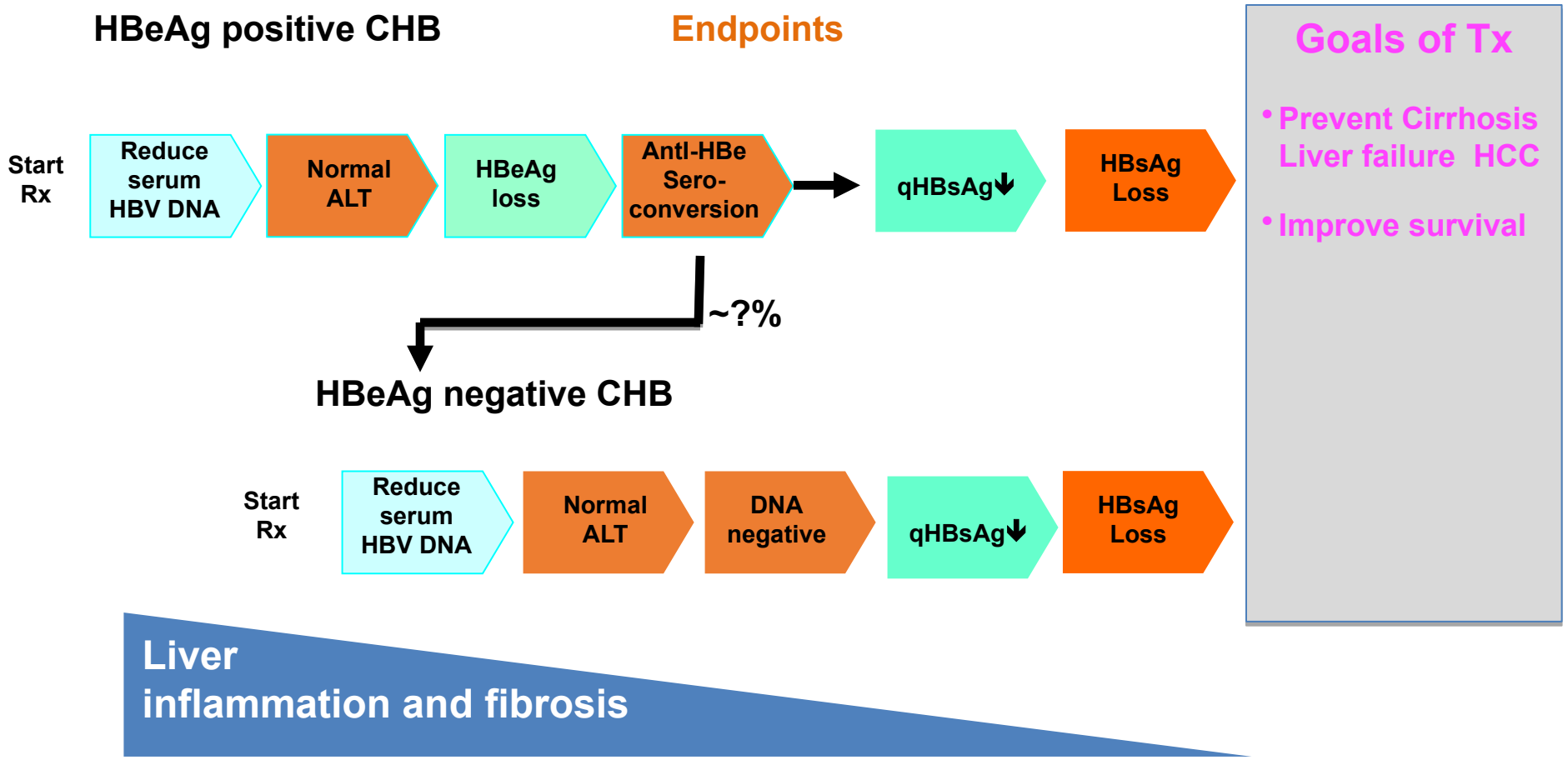


Death

Fattovich *et al*. *Hepatology* 1995; Liaw *et al*. *Liver* 1989; Ikeda *et al*. *J Hepatol* 1998.

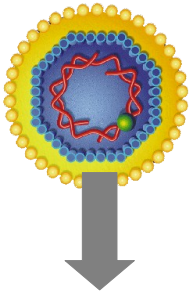
Should We Treat All CHB patients?

Goals are to reduce disease progression



Chronic Hepatitis B: Risk Factors for Disease Progression

Age (Increasing risk with age)

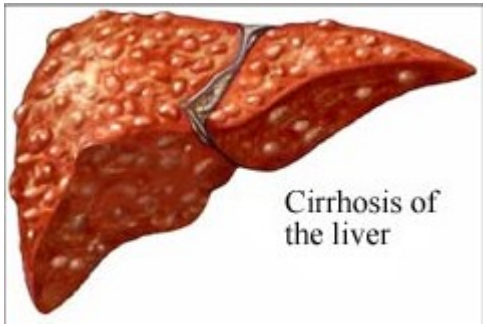


Elevated viral load

(Biological risk gradient with increasing HBV DNA)

Family History

Gender (M > F)



HBeAg status

(Increases risk of HCC)

Presence of hepatic inflammation / fibrosis

(Increases risk of HCC)

Alcohol consumption

(Increases risk of HCC)

HBV Genotype

(Genotype C > B in Asians)

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

How to determine who is at risk of disease progression?

Cohort/prognostic study

Characteristics of good prognostic study

- Large size
- Clear entry criteria
- Prospective
- Community based
- Well defined endpoints
- Large number of events
- Few dropouts
- Sufficient duration of followup

Systematic Review

Characteristics of a good systematic review/meta-analysis

- Large effect size may overcome the potential risk of bias of cohort studies
- Precision (narrow confidence intervals)
- Consistency of effect
- Low risk of bias
- High quality studies
- Low heterogeneity

However, no single prognostic study is ideal
Hence the best data comes from Systematic Reviews

What is a guideline?

"Guidelines are recommendations intended to assist providers and recipients of health care and other stakeholders to make informed decisions. Recommendations may relate to clinical interventions, public health activities, or government policies."

WHO 2003, 2007

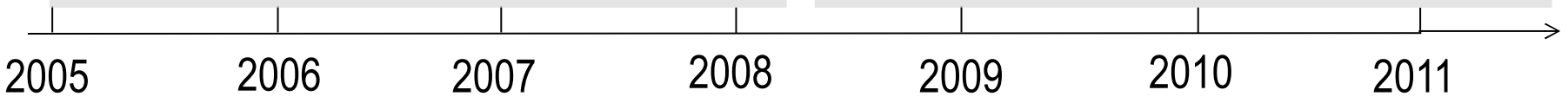
GRADE Working Group
Grades of Recommendation Assessment, Development and Evaluation

- Aim: to develop a common, transparent and sensible system for grading the quality of evidence and the strength of recommendations (over 100 systems)
- International group of guideline developers, methodologists & clinicians from around the world (>200 contributors) – since 2000
- International group: ACCP, AHRQ, Australian NMRC, BMJ Clinical Evidence, CC, CDC, McMaster Uni., NICE, Oxford CEBM, SIGN, UpToDate, USPSTF, WHO

CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, Chest 2006, BMJ 2008

70+ Organization Globally have adopted GRADE

- World Health Organization
- CDC-ACIP
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- American Thoracic Society
- American College of Physicians
- European Respiratory Society
- European Society of Thoracic Surgeons
- British Medical Journal
- Infectious Disease Society of America
- UpToDate®
- American College of Chest Physicians
- National Institutes of Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- Cochrane Collaboration
- Infectious Disease Society of America
- Clinical Evidence
- Agency for Health Care Research and Quality (AHRQ)
- Over 70 (major) organizations



GRADE APPROACH

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

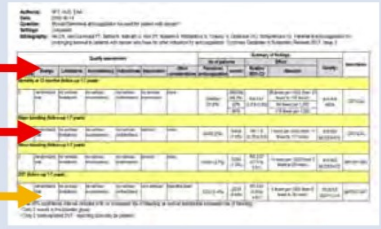
P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Not important



Summary of findings & estimate of effect for each outcome

High
Moderate
Low
Very low

Randomization increases initial quality

Grade down

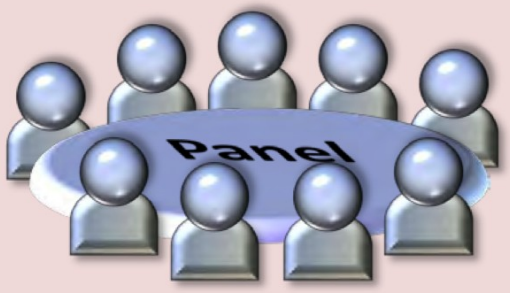
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Systematic review

Guideline development



Grade
overall quality of evidence
across outcomes based on
lowest quality
of ***critical*** outcomes

Formulate recommendations:

- For or against (direction)
- Strong or conditional/weak (strength)

By considering:

- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences

Revise if necessary by considering:

- ❑ Resource use (cost)

- "We recommend using…"
- "We suggest using…"
- "We recommend against using…"
- "We suggest against using…"

Quality of Evidence

AASLD†[13]	APASL 2015[12]	EASL 2017[11]	WHO[3]
High/moderate quality: RCT Low/very low quality: Observational data	High quality (A): Meta-analysis or RCTs or high quality observational studies. Further research is very unlikely to change effect Moderate quality (B): Low quality randomized trials; upgraded observational studies. Further research may change the effect Low quality (C): observational studies. Very low quality (C): Non randomized trials; observational studies with risk of bias; case series/case reports. Further research is very likely to change the estimate.	I: Randomised, controlled trials II-1: Controlled trials without randomisation II-2: Cohort or case-control analytical studies II-3: Multiple time series, dramatic uncontrolled experiments III: Opinions of respected authorities, descriptive epidemiology	The GRADE system classifies the quality of evidence as high, moderate, low and very low. RCTs are initially rated as high-quality evidence but may be downgraded for several reasons, including the risk of bias, inconsistency of results across studies, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if multiple studies show the same effect,

Strength of recommendation

AASLD†[13]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Strong recommendation: • Population: Almost all people in this situation agree • Health care workers: Almost all people agree. • Policy makers: Can be adapted as a policy in most situations. Conditional recommendation: • Population: Most people people agree, but many would not. • Health care workers: Assist patients to decide consistent with their values. • Policy makers: There is a need for substantial debate and involvement of stakeholders	Strong recommendation (1): Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost. Weaker recommendation (2): Variability in preferences and values or greater uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	1: Strong recommendation. Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost. 2: Weaker recommendation. Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	A strong recommendation: The desirable effects of outweigh the undesirable effects. A conditional recommendation The desirable effects probably outweigh the undesirable effects but not confident about trade-offs. Not all would accept the recommendation. The reasons for making a conditional recommendation include the absence of high-quality evidence, imprecision in outcome estimates, uncertainty regarding how individuals value the outcomes, small benefits, and benefits that may not be worth the costs (including the costs of implementing the recommendation).

Guideline Development

Guideline	AASLD†[13]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Formulation of questions to be answered by guideline	Specific questions were specified a priori for evaluation by the guidelines committee, although not PICO based (population, intervention, comparison, outcomes) format.	Process not explicitly stated.	Process not explicitly stated.	An initial scoping and planning process to formulate question using PICO format and ranked
Search for evidence	AASLD content experts worked with a systematic review group to synthesize the available evidence. They finalized evidence summaries using the GRADE approach.	Manuscripts and abstracts through January 2015 were were evaluated. If evidence was unavailable, on the experts' personal experience and opinion after deliberations.	Evidence from existing publications was used, and, if evidence was unavailable, on the experts' personal experience and opinion. Manuscripts and abstracts through January 2015 were were evaluated.	Systematic reviews and meta-analyses were commissioned to external group experienced in systematic reviews. They finalized evidence summaries using the GRADE approach.

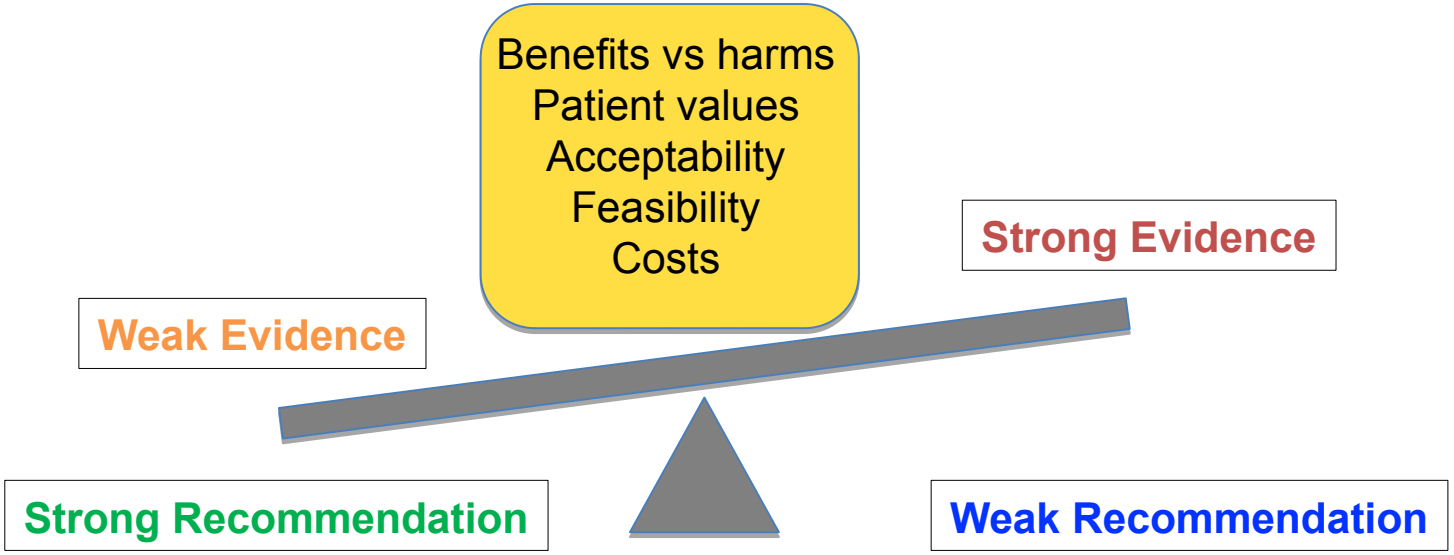
WHO PICO Questions

PICO 2a Who to Treat?	Among HBsAg-positive persons, what factors/tests best identify individuals at highest risk of progression, as well as those at very low risk of progression?
P	HBsAg-positive persons
I	Key permutations of key baseline risk factors from studies of prognosis: clinical factors only (age, cirrhosis/fibrosis); clinical plus ALT: clinical plus ALT and HBV DNA: Sample stratifications include: age >40 vs <40 years; HBeAg-positive vs -negative; cirrhosis (compensated or decompensated) vs no cirrhosis; fibrosis (METAVIR 1-3) vs no fibrosis; HBV DNA (any positive or unknown, or >2000 or >20 000 IU/mL or >106 copies/mL) vs undetectable; ALT (>2x ULN or >ULN) vs normal
C	Absence of these baseline factors
O	Liver-related morbidity (fibrosis, cirrhosis, end-stage liver disease, hepatocellular carcinoma); progression of liver disease; mortality
T	Annual progression and mortality

PICO 2b Who to Treat?	Among HBsAg-positive persons, what factors/tests best identify individuals with greatest benefit of treatment, and least benefit from treatment in those with and without access to laboratory tests?
P	HBsAg-positive persons stratified according to key baseline prognostic factors and : clinical factors only (age, cirrhosis/fibrosis); clinical plus ALT: clinical plus ALT and HBV DNA: sample stratifications include: Age >40 vs <40 years; HBeAg positive vs. negative; cirrhosis (compensated or decompensated) vs no cirrhosis; Fibrosis (METAVIR 1-3) vs no fibrosis; HBV DNA (any positive or unknown, or >2000 or >20 000 IU/mL or >106 copies/mL) vs undetectable; ALT (>2x ULN or >ULN) vs normal
I	HBV antiviral treatment
C	No HBV treatment
O	reversion of fibrosis stage; mortality; severe adverse effects; antiviral resistance
T	Annual progression and mortality

WHO Guidelines 2017, appendix 2: Systematic Review Reports & Evidence Based Summaries

Strength of Evidence vs Strength of Recommendation



<u>Weak Evidence but Strong Recommendation</u>

- Situation where evidence is not of high quality but treatment potentially lifesaving

<u>Strong Evidence but Weak Recommendation</u>

- Situation where the evidence is high quality but the benefit may be marginal or not cost effective or has potential harm

Indications for Treatment: HBeAg positive CHB

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
HbeAg positive CHB	• ALT >2 ULN or evidence of significant histologicaldisease plus elevated HBV DNA above 20,000 IU/ mL (Quality of Evidence: Moderate; strength of Recommendation: Strong). • Adults >40 years of age with normal ALT and elevated HBV DNA (>1,000,000 IU/mL)and liver biopsy showing significant necroinflammation or fibrosis (Quality and of Evidence: Very Low; strength of Recommendation: Conditional).	• HBV DNA>20,000 IU/mL and persistent ALT>2 ULN or significant inflammation/fibrosis. (B1) • ALT 1-2X ULN: Biopsy should be considered if non-invasive tests suggest evidence of significant fibrosis, age> 35 years, ALT persistently elevated, or there is a family history of HCC or cirrhosis. Treat, if moderate to severe inflammation or significant fibrosis. (B1)	• HBV DNA>2,000 IU/ ml, ALT>ULN and/or at least moderate liver necroinflammation or fibrosis (Evidence level I, grade of recommendation 1). • Adults>30 years with normal ALT and high HBV DNA levels may be treated regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).	• Treatment is recommended for adults with CHB without cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU), regardless of HBeAg status (Strong recommendation, moderate quality of evidence).

Indications for Treatment: HBeAg negative CHB

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
HBeAg negative CHB	• ALT >2 ULN or evidence of significant histological disease plus elevated HBV DNA > 2,000 IU/mL. • ALT 1-2X ULN with significant fibrosis. Persistent ALT>ULN but <2 ULN with HBV DNA> 2000 IU/ mL (Quality of Evidence: Moderate; strength of Recommendation: Strong).	• HBV DNA>2,000 IU/ mL and ALT>2 ULN or significant inflammation/fibrosis . (B1) • ALT 1-2X ULN: Biopsy should be considered if non-invasive tests suggest evidence of significant fibrosis, age> 35 years, ALT persistently elevated, or there is a family history of HCC or cirrhosis. Treat, if moderate to severe inflammation or significant fibrosis. (B1)	• HBV DNA>2,000 IU/ ml, ALT>ULN and/or at least moderate liver necroinflammation or fibrosis (Evidence level I, grade of recommendation 1).	• CHB without cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU), regardless of HBeAg status (Strong recommendation, moderate quality of evidence).

Indications for Treatment: Cirrhosis

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Cirrhosis	Patients with viremia (even <2,000 IU/mL) should be treated with antiviral therapy (Quality and Certainty of Evidence: Very Low; strength of Recommendation: Conditional).	HBV DNA>2000 mL for compensated cirrhosis (C2). HBsAg positive patients with decompensated cirrhosis and detectable HBV DNA require immediate antiviral treatment with NA(s) (A1).	Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).	As a priority, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. (Strong recommendation, moderate quality of evidence)

Indications for Treatment: Pregnancy

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Pregnancy	HBV DNA level >200,000 IU/mL at 28-32 weeks of gestation (Quality of Evidence: Low; strength of Recommendation: Conditional).	HBV DNA above 6–7 log10 IU/ml from week 28-32 of gestation. NAs can be administered after discussion with the patient, even in patients with lower DNA levels (B2).	HBV DNA levels 200,000 IU/ml or HBsAg levels [4 log10 IU/ml, antiviral prophylaxis with TDF should start at week 24–28 of gestation (Evidence level 1, grade of recommendation 1).	No recommendation

Indications for Treatment: Co-infection

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
HCV co-infection	Same criteria as mono-infected patients.	Same criteria as mono-infected patients. (A1).	Same criteria as mono-infected patients. (Evidence level II, grade of recommendation 1). HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA and monitored closely (Evidence level II-2, grade of recommendation 2).	Same criteria as mono-infected patients.
HDV co-infection	If HBV-DNA levels are elevated, concurrent therapy with NA using preferred drugs (entecavir, TDF, or TAF).	In patients with coinfection of HBV and HDV, determine which virus is dominant and treat accordingly with pegIFNa for 12–18 months. (A1).	In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1).	-
HIV co-infection	Patients who are already receiving effective ARVT that does not include a drug with antiviral activity against HBV should have treatment changed to include TDF or TAF with emtricitabine or lamivudine.	Tenofovir combined with emtricitabine or lamivudine plus a third agent active against HIV should be used (A1).	HIV-HBV co-infected patients should be treated with a TDF or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).	In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all with a CD4 count ≤500 cells/mm3, regardless disease stage (Strong recommendation, low quality of evidence).

Indications for Treatment: Children

Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Children	Antiviral therapy in chronic hepatitis B (CHB) HBeAg-positive children (ages 2 to <18 years) with both elevated ALT and measurable HBV-DNA levels, with the goal of achieving sustained HBeAg seroconversion. (Quality and Certainty of Evidence: Moderate; strength of Recommendation: Conditional).	Patients with moderate to severe activity or significant fibrosis with any ALT level should be considered for treatment (A1). Treatment may be started in pre-cirrhotic chronic HBV-infected patients if they have persistently elevated ALT levels [2 times upper limit of normal (ULN) (at least 1 month between observations) and HBV DNA [20,000 IU/ml if they are HBeAg-positive and [2000 IU/ml if HBeAg-negative, even without a liver biopsy (B1).	In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and Peg IFNa can be used in this population (Evidence level II-2, grade of recommendation 2).	Children with CHB and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels. (Strong recommendation, moderate quality of evidence) The FDA has approved tenofovir for use in adolescents and children above the age of 12 years for HBV treatment (and 3 years or older for HIV treatment). FDA has approved entecavir for children with CHB above 2 years of age.

Indications for Treatment: immune suppressed

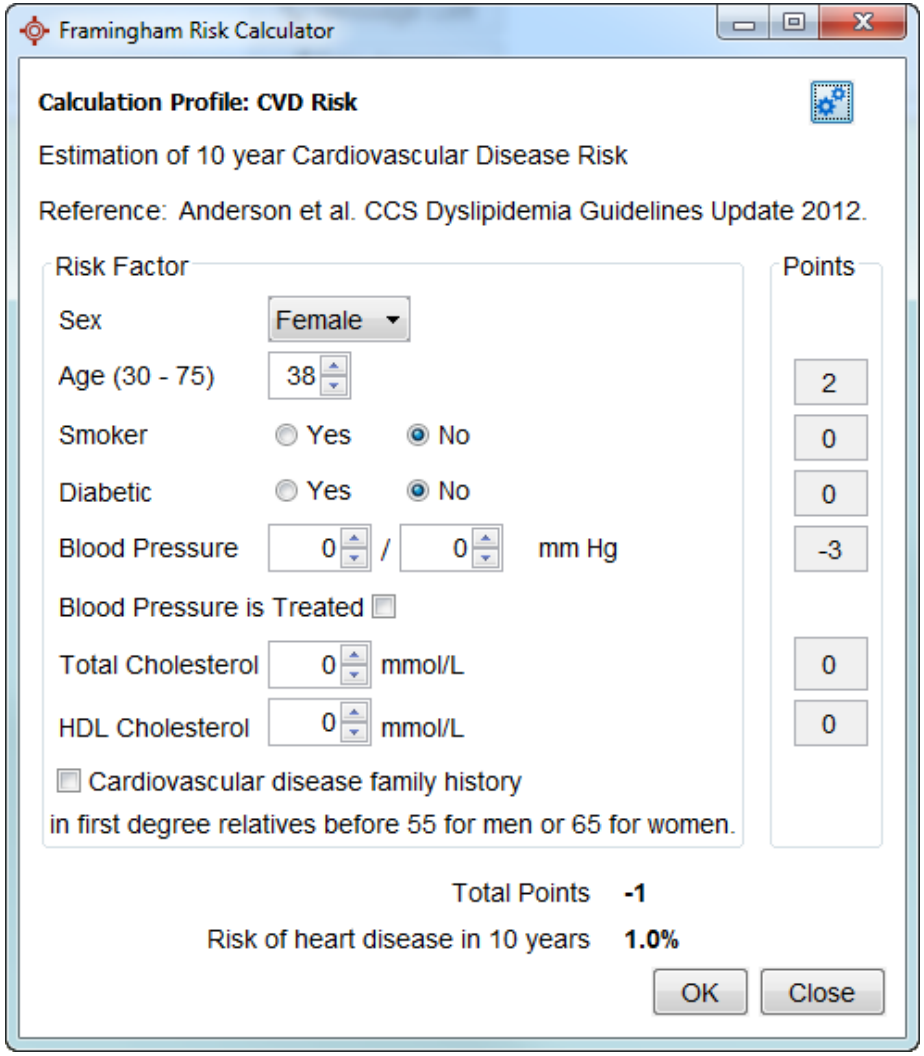
Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Liver transplant recipients	HBsAg-positive patients undergoing liver transplantation should receive prophylactic therapy with NAs ± HBIG†. Patients who receive HBsAg-negative but anti-HBc–positive grafts should receive long-term NAs†.	Among low risk patients (i.e., with undetectable HBV DNA levels at the time of transplant), HBIG free regimens can be used. High potency NAs (entecavir or tenofovir) should be used for life (B1).	NA± HBIG is recommended after liver transplantation (Evidence level II-1, grade of recommendation 1). HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA (Evidence level II-2, grade of recommendation 1).	-
Recipients of immunosuppressive/ cytotoxic therapy	HBsAg-positive patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy†. HBsAg-negative, anti-HBc–positive patients receiving anti-CD20 antibody therapy or undergoing stem cell transplantation should be treated with NAs†.	Prophylactic anti-viral therapy should be given to HBsAg positive cancer patients who receive cytotoxic or immunosuppressive therapy (A1). Physicians should be aware of the risk of HBV reactivation in HbsAg negative, HBc-positive patients receiving rituximab (B1).	All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis (Evidence level II-2, grade of recommendation 1). HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-2, grade of recommendation 1).	-

Indications for Treatment: Miscellaneous

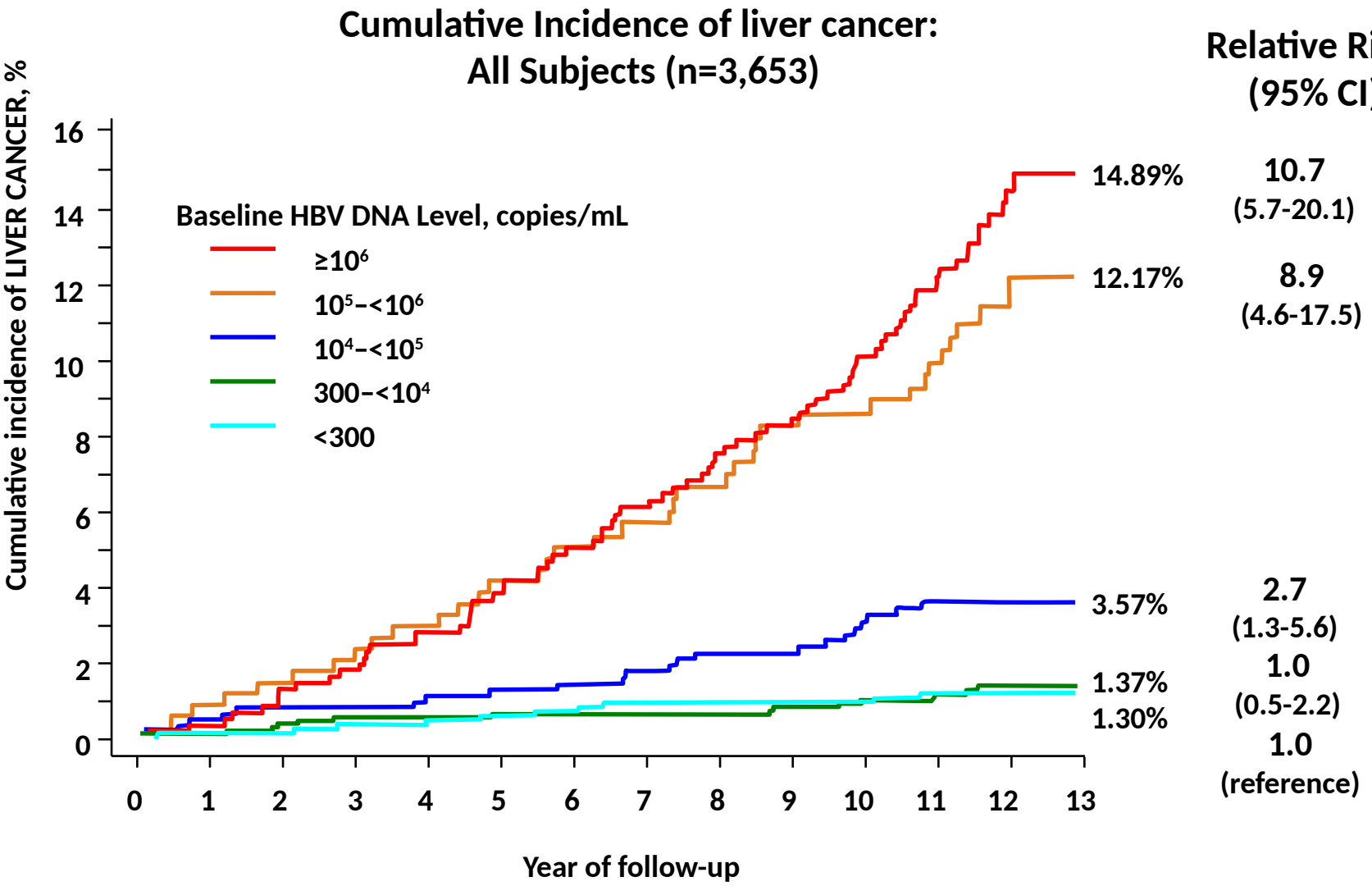
Guideline	AASLD 2016[10]	APASL 2015[12]	EASL 2017[11]	WHO[3]
Acute Hepatitis B	Only if acute liver failure or who have a protracted, severe course, as indicated by total bilirubin >3 mg/dL international normalized ratio >1.5, encephalopathy, or ascites†.	Treatment is only indicated for patients with fulminant hepatitis B or for those with severe or protracted acute hepatitis B (C2).	Only patients with severe acute hepatitis B, characterised by coagulopathy or protracted course, should be treated with NA (Evidence level II-2, grade of recommendation 1).	Persons with fulminant or severe acute hepatitis may benefit from NA therapy with entecavir or tenofovir, to improve survival and reduce the risk of recurrent hepatitis B.
Extrahepatic manifest.	Indication for treatment independent of liver disease severity†.	HBsAg positive patients with extra-hepatic manifestations and active HBV replication may respond to antiviral therapy (B1).	Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA (Evidence level II-2, grade of recommendation 1).	HBsAg-positive persons with HBV-related extrahepatic manifestations and active HBV replication may respond to NA antiviral therapy.
Family history of HCC	Consider treating in patients with a family history of HCC or cirrhosis, even if ALT<2 ULN and HBV DNA below threshold†.	Liver biopsy if patient does not reach the ALT or HBV DNA threshold for treatment. Treat if moderate to severe inflammation or significant fibrosis. (C1)	Patients with family history of HCC or cirrhosis can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).	No recommendation

The Future of Patient Selection for Therapy

- Cardiac Risk Calculator



REVEAL study: High HBV viral load is associated with increased incidence of liver cancer

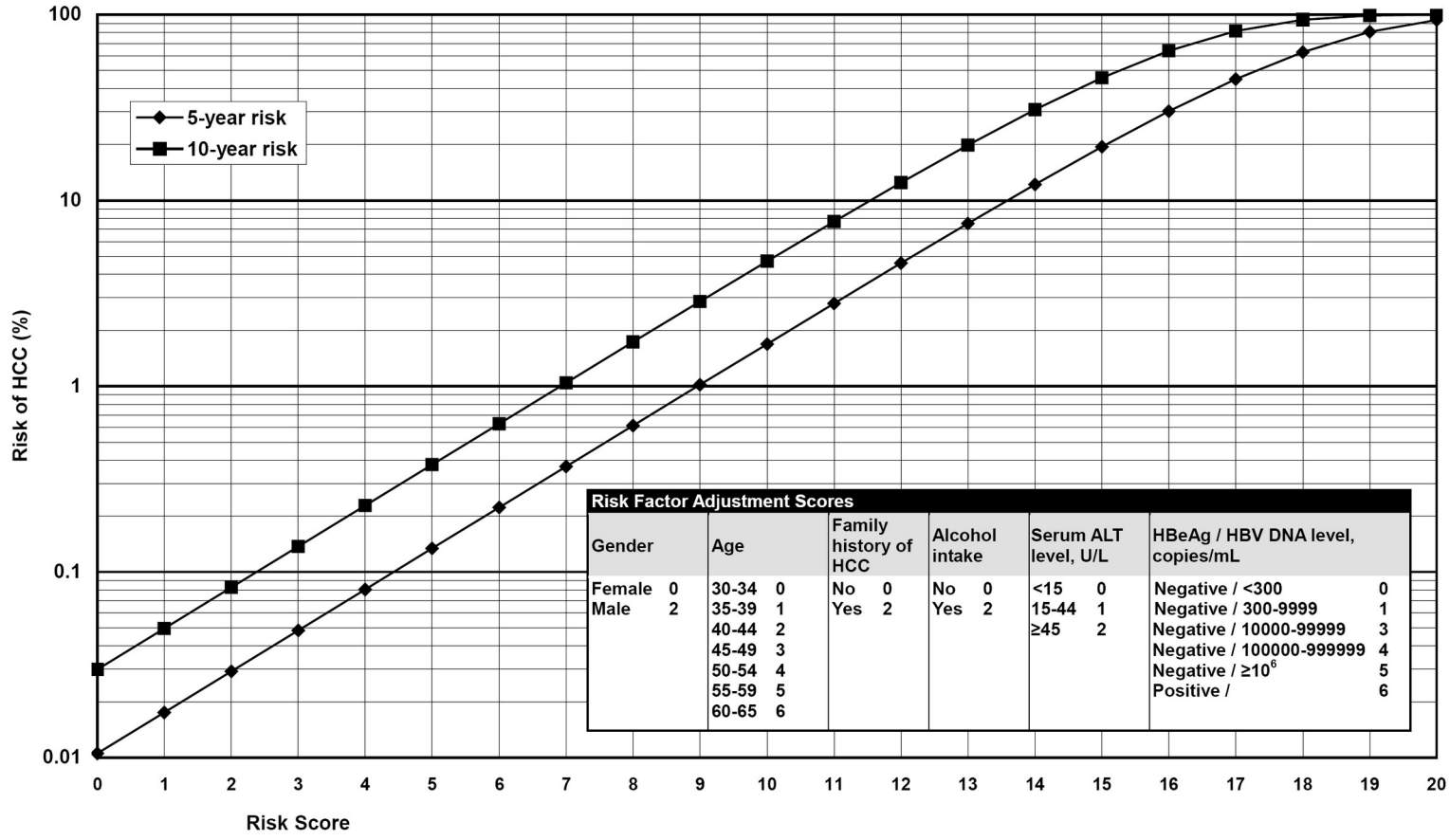


Chen et al, JAMA 2006; 295: 65-73

REVEAL Risk Calculator

Risk predictor	β -coefficient	P value	Risk score
Gender			
Female	Referent		0
Male	0.90474	0.002	2
Age (5-yr increament)	0.50839	<0.001	1
Family history of HCC			
No	Referent		0
Yes	0.94955	0.008	2
Alcohol consumption			
No	Referent		0
Yes	0.77901	<0.001	2
Serum ALT level, U/L			
<15	Referent		0
15-44	0.53547	0.026	1
≥45	0.93059	0.003	2
HBeAg/HBV DNA level, copies/mL			
Negative/<300 (Undetectable)	Referent		0
Negative/300-9999	0.44098	0.44	1
Negative/10000-99999	1.71424	<0.001	3
Negative/100000-999999	2.18915	<0.001	4
Negative/10^6	2.65376	<0.001	5
Positive	3.12010	<0.001	6

Prognostic Risk based on REVEAL Risk Calculator



Risk Factor Adjustment Scores

Gender		Age		Family history of HCC		Alcohol intake		Serum ALT level, U/L		HBeAg / HBV DNA level, copies/mL	
Female	0	30-34	0	No	0	No	0	<15	0	Negative / <300	0
Male	2	35-39	1	Yes	2	Yes	2	15-44	1	Negative / 300-9999	1
		40-44	2					≥45	2	Negative / 10000-99999	3
		45-49	3							Negative / 100000-999999	4
		50-54	4							Negative / $\geq 10^6$	5
		55-59	5							Positive /	6
		60-65	6								

Yang HI et al. JCO 2010;28:2437-2444

Why not use REVEAL Risk Calculator?

- Unclear if applicable to Caucasians and non-Asians
- REVEAL population >40y, mainly HBeAg neg
- Most importantly:
  - Treatment Benefit NOT demonstrated
  - No RCT showing that patients who fulfill REVEAL risk score will benefit with regards to clinically significant outcomes: mortality, HCC reduction and reduction in CHB outcomes

Conclusions

- The development of Guidelines is now a structured process with the global standard being GRADE, relying on systematic reviews to provide the highest quality of evidence
- The WHO and AASLD have structured scoping questions and systematic reviews in their guidelines
- Although there are some differences between AASLD, EASL, APASL and WHO guidelines, in general they are in agreement
- In the future, use of Risk Calculators may simplify selection of patients suitable for therapy
- The goal of current guidelines is to reduce disease progression and mortality, as the likelihood of cure is low but this may change with treatments that can achieve functional cure, which then will supercede use of risk calculators