The Chronic Liver Disease Foundation (CLDF) and the International Coalition of Hepatology Education Providers (IC-HEP) present:

THE LIVER SUMMIT

Certified by:

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER

Provided by:

CLDF
Chronic Liver Disease Foundation

Endorsed by:

ICHEP
International Coalition of Hepatology Education Providers

Learning Objectives

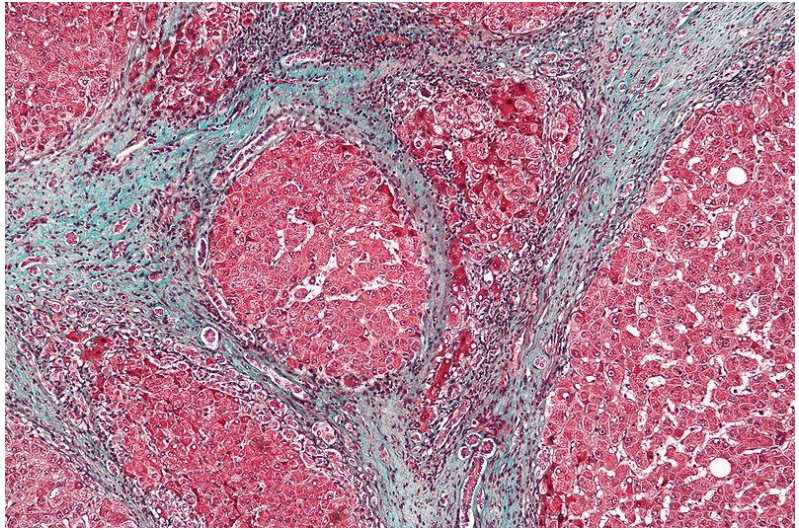
- Identify the risk factors and symptoms of chronic liver disease
- Discuss laboratory tests and invasive/noninvasive methodologies used to ascertain the underlying cause and classify the stage of disease
- Describe screening and treatment for patients with cirrhosis/hepatocellular carcinoma
- Apply the AASLD guidelines on screening, diagnosis, and treatment of patients infected with chronic hepatitis C
- Recognize the safety and efficacy of currently available HCV therapies and those expected in the next 6 months and advise patients regarding treatment options based on their individual characteristics

Cirrhosis: Diagnosis and Management

Outline

- Diagnosis
- Prevalence
- Staging and Prognosis
- Complications of Cirrhosis
- Hepatic Encephalopathy

Cirrhosis



- Accumulation of collagen deposition = fibrosis ➔ cirrhosis
- Final common pathway for most chronic liver diseases
- Histologically often indistinguishable from one another
- Note the loss of central venules, loss of the hepatic acinus, many regenerative nodules
- Former terms “micronodular” or “macronodular” largely abandoned
- “Liver Cirrhosis” is redundant

From http://digestive.niddk.nih.gov/ddiseases/pubs/cirrhosis/. Accessed January 2014.
Trichrome stain micrograph from http://en.wikipedia.org/wiki/Cirrhosis. Accessed January 2014.

Cirrhosis: Symptoms and Signs

- Anorexia, weight loss
- Weakness, fatigue
- Muscle loss, cramps
- Nausea
- Vague (RUQ) abdominal pain
- Pruritus
- Easy bruising, epistaxis
- GI bleeding
- Confusion, sleep disturbance
- Amenorrhea or irreg menses

- Spider angiomata
- Palmar erythema
- Gynecomastia, testicular atrophy
- Abdominal distention, edema
- Parotid hypertrophy
- Dupuytren's contractures
- Clubbing, leukonychia
- Jaundice, icterus
- Caput medusa
- Splenomegaly
- Enlarged left or caudate lobe
- Asterixis, fetor hepaticus
- Cachexia

However…..often asymptomatic

Cirrhosis: Diagnosis

- Gold standard remains liver biopsy
- Biopsy not required for all, “Clinical or radiologic cirrhosis”
- Clues: physical exam, abdominal imaging, low platelet count, AST:ALT ratio >1, cholestasis, low albumin, prolonged INR
- Non-invasive assays (FibroTest, APRI, FIB-4)
- U/S Elastography (FibroScan, Aixplorer), Magnetic Resonance Elastography
- Beware of non-cirrhotic portal hypertension

Transient Elastography

- Works by measuring shear wave velocity
- Non-invasive
- High concordance with biopsy
- Also effective in predicting portal hypertension
- Eliminates the need for biopsy in some patients

Afdhal NH. *Gastroenterol Hepatol (NY)* 2012;8:605-607.

Technical Limitations of Transient Elastography

- Ascites
- Morbid obesity
- Adipose tissue within the chest wall
- Acute hepatitis
- Congestive hepatopathy
- Post-prandial variability

Afdhal NH. *Gastroenterol Hepatol (NY)* 2012;8:605-607.

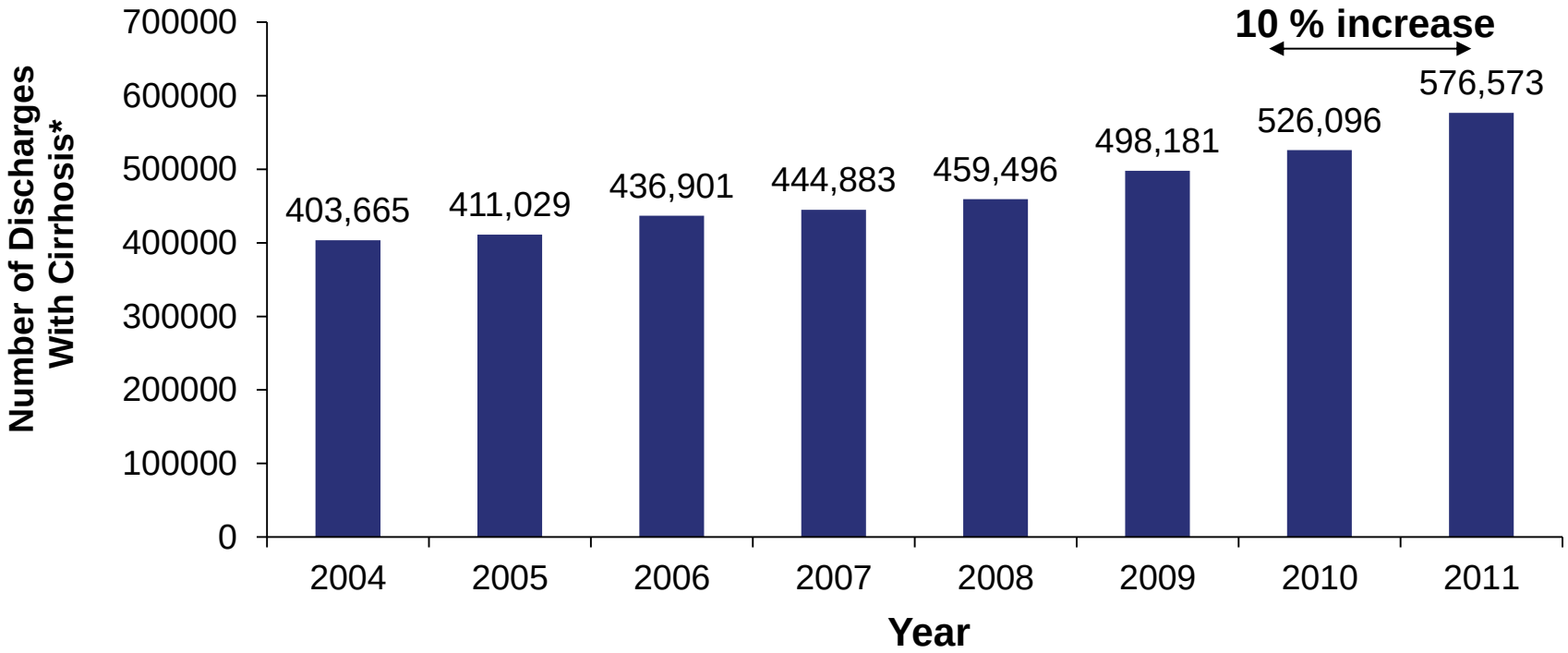
Prevalence

Prevalence of Cirrhosis

- Experts estimate that 5.5 million people in the United States have cirrhosis
- Many cirrhotics remain undiagnosed
  - 40% of cases of cirrhosis “latent”
- Twelfth leading cause of death in US

Khungar V, Poordad F. *Clin Liver Dis* 2012;16:73-89.

US Hospital Discharges Due to Cirrhosis Are Increasing

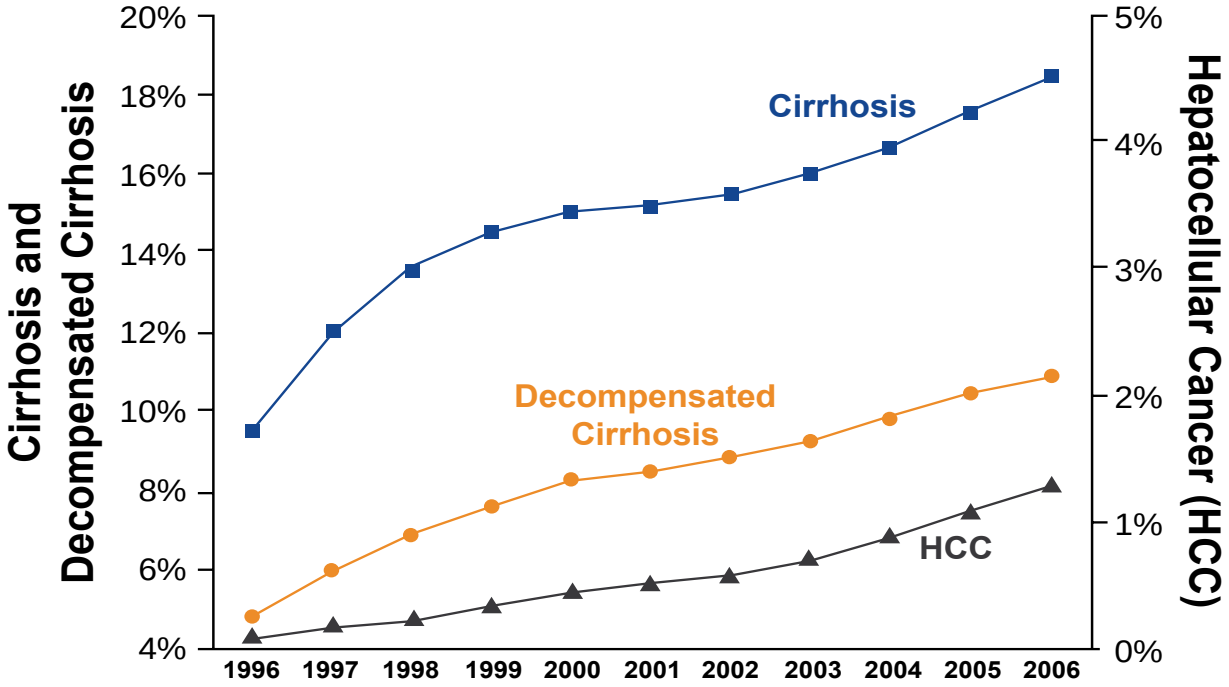


*ICD-9-CM diagnosis codes 571.2. 571.5, 571.6; all listed diagnoses.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. http://hcupnet.ahrq.gov. Accessed January 2014

Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans



El-Serag HB. *Gastroenterology* 2012;142:1264–1273.

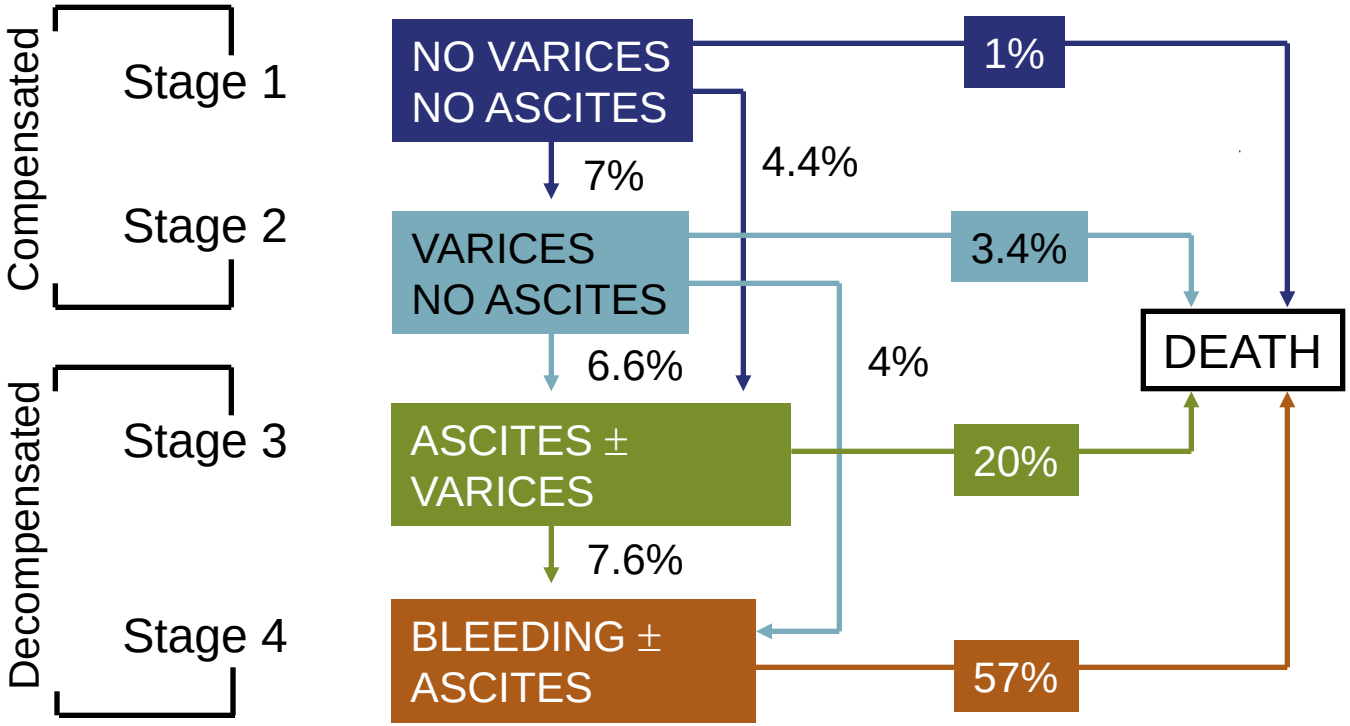
Disease Severity and Prognosis

Stages of Cirrhosis

Stage	Definition	1-year mortality
1	Compensated **without varices**	1%
2	Compensated **with varices**	3%
3	Decompensated with ascites **without variceal hemorrhage**	20%
4	Decompensated with or w/out ascites **with variceal hemorrhage**	57%

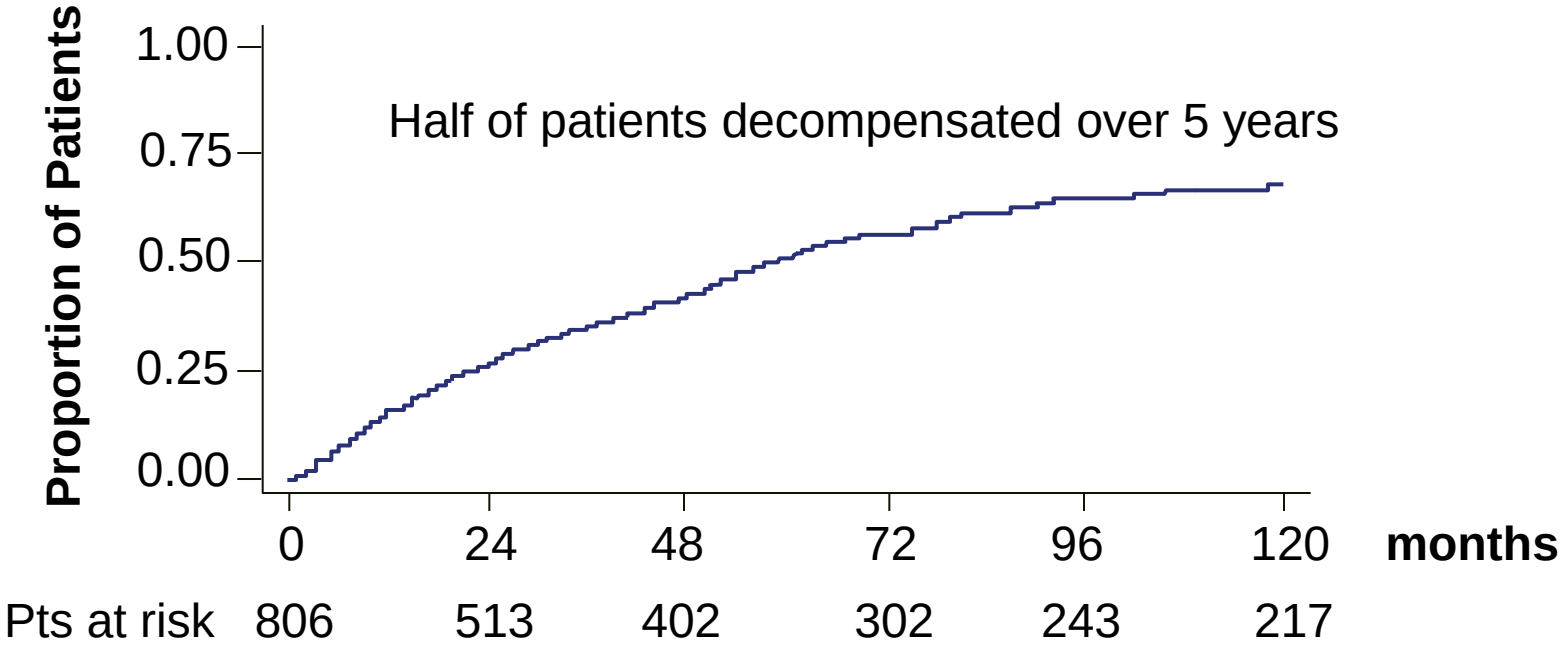
D'Amico G et al. *J Hepatol*. 2006;44:217-231.

Baveno IV International Consensus Workshop Staging System for Cirrhosis: 1-Year Outcome Probabilities



D'Amico G et al. *J Hepatol*. 2006;44:217-231.

Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Cirrhosis Over Time



D'Amico G et al. *J Hepatol*. 2006;44:217-231.

Classification of Cirrhosis: Child-Turcotte-Pugh (CTP)

	Points		
	1	2	3
Encephalopathy	None	Grade 1 – 2 (or precipitant-induced)	Grade 3 – 4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8 - 3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Total Numerical Score	Child-Pugh Class
5 - 6	A
7 - 9	B
10 - 15	C

Class A considered "compensated"

Class B/C considered "decompensated"

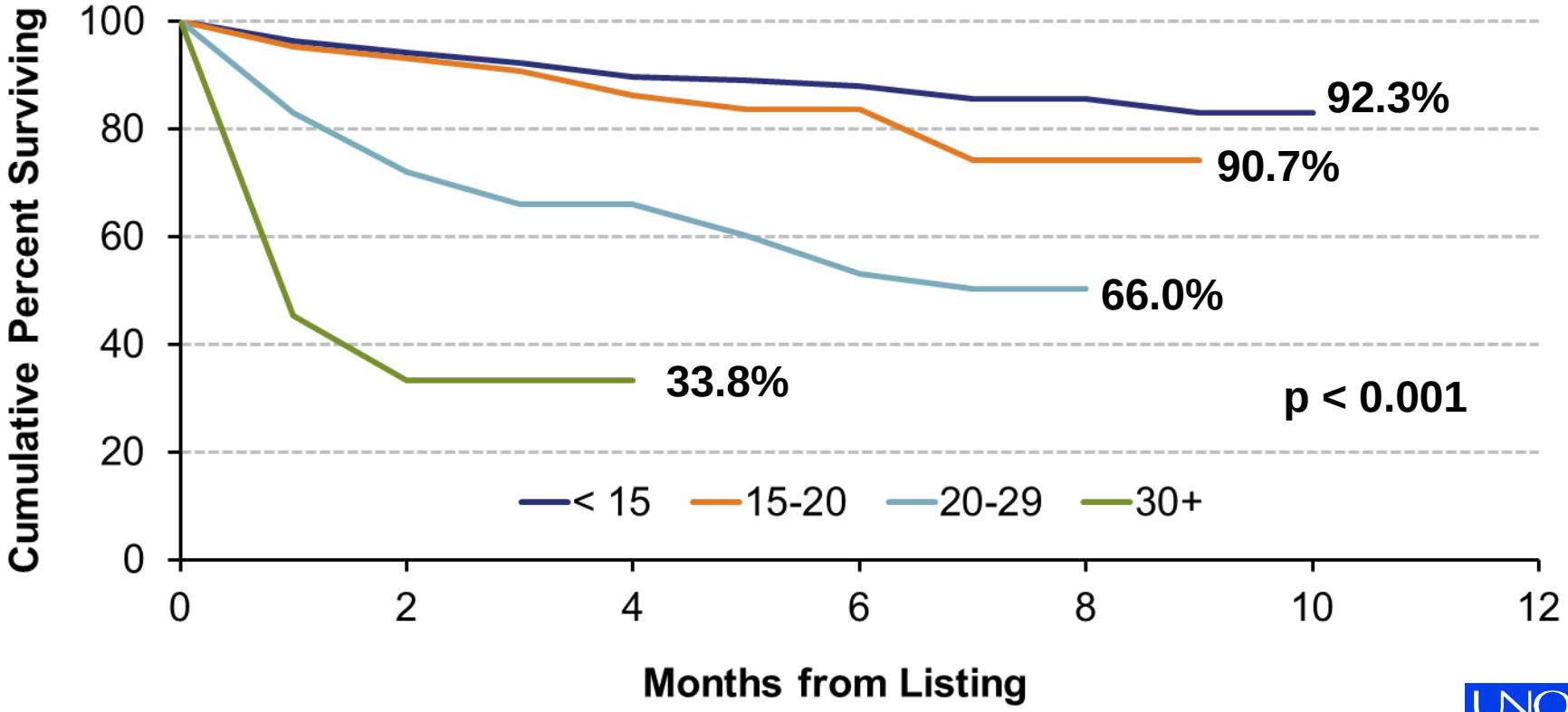
Adapted from Garcia-Tsao G et al. *Am J Gastroenterol.* 2009;104:1802-1829.

Classification of Cirrhosis Severity
Model for End Stage Liver Disease Score

- Calculated from 3 variables:
  - INR
  - Bilirubin
  - Serum creatinine
- The MELD score equation:
  - [9.6 x $\log_e$ creatinine (mg/dL) + 3.8 x $\log_e$ bilirubin (mg/dL) + 11.2 x $\log_e$ INR + 6.4]
- Eliminates subjectivity of HE and ascites evaluation used in CTP
- Etiology removed without affecting predictive ability

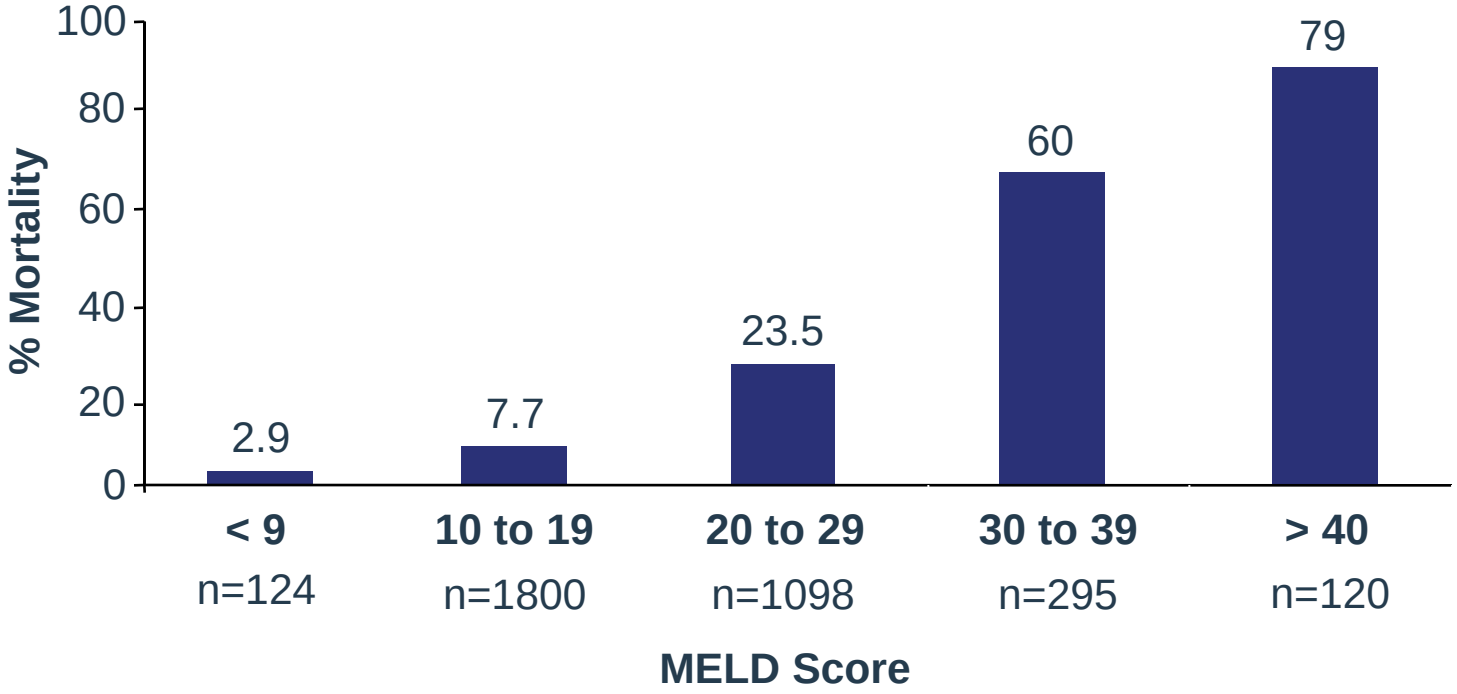
Murray KF, Carithers RL. *Hepatology* 2005;41:1-26.
Wiesner R et al. *Gastroenterology* 2003;124:91-96.

MELD and Survival



UNOS

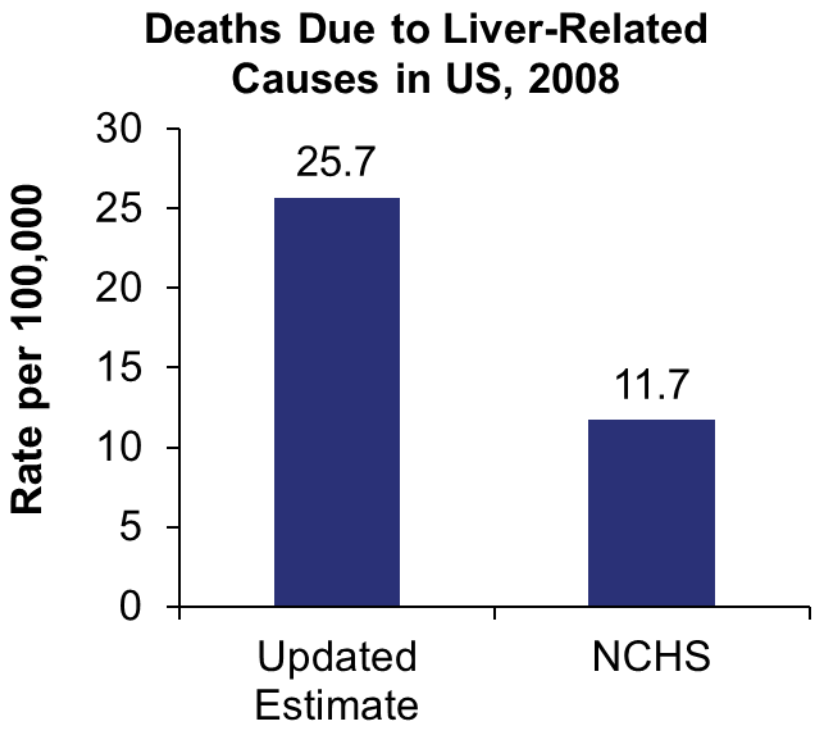
MELD Score: 3 Month Mortality**



Wiesner, R et al. *Gastroenterology* 2003; 124:91-96

**Mortality includes death on waitlist and removed for "too sick"

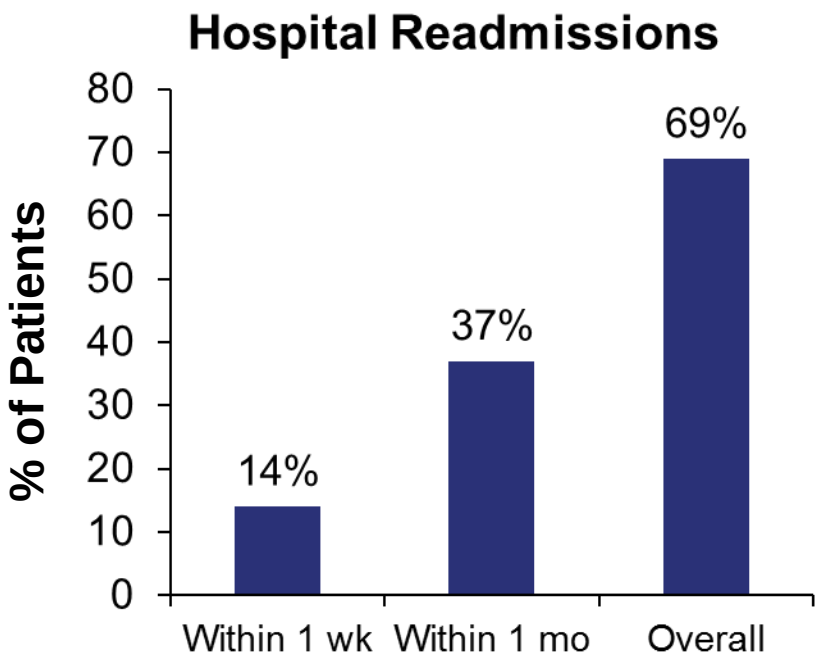
Liver-Related Mortality in the US is Underestimated



- Liver related mortality in the United States is underestimated by the National Center for Health Statistics (NCHS), in part, as a result of incomplete inclusion of liver-related deaths
- Use of an updated definition of liver mortality increased the estimated death rate by >2 fold from 11.7 to 25.7 deaths/100,000

Asrani, SK et al. *Gastroenterology* 2013;145:375-382.

Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common

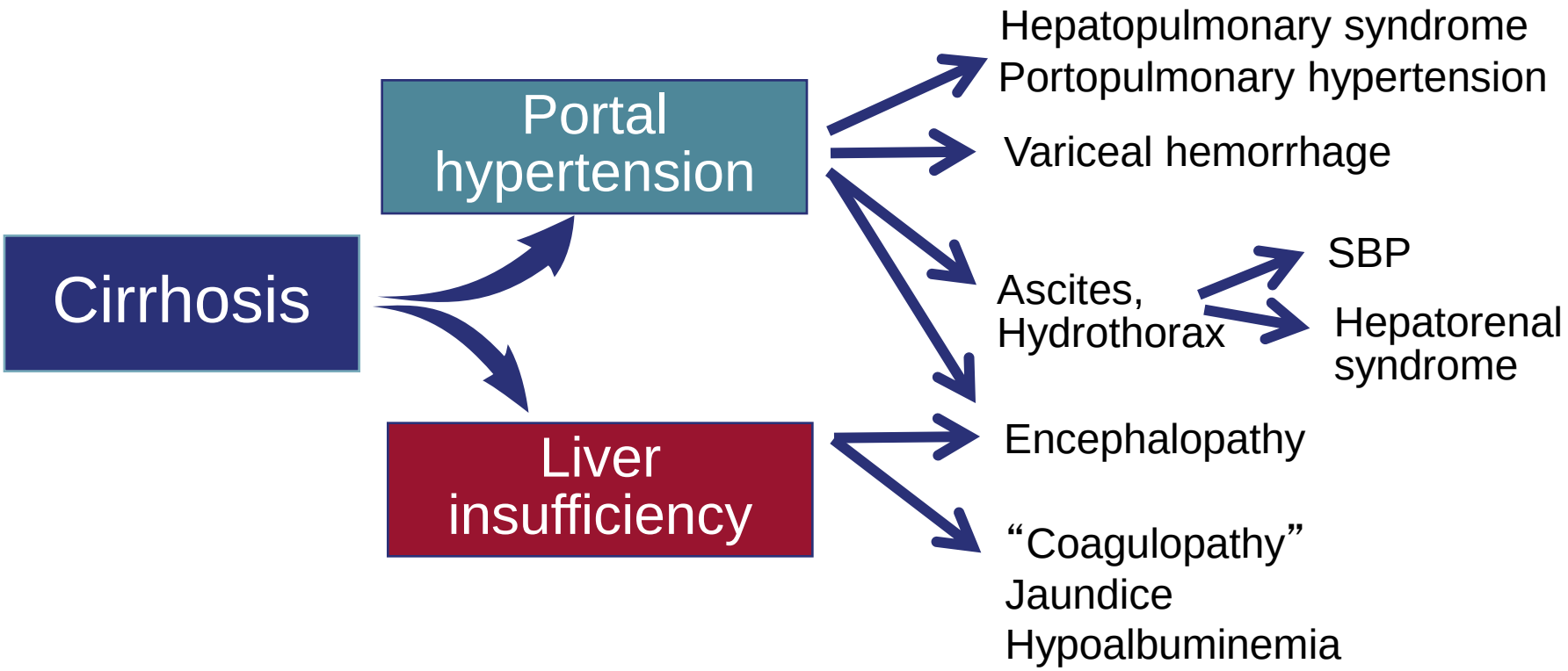


- Retrospective study of 402 patients from an academic transplant center
- Follow-up time censored at death, elective admissions such as transplant or post-procedure observation, or the date of last clinic note; median follow-up was 203 days
- Included cirrhotic patients hospitalized for ascites, SBP, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to readmission was 67 days
- Median number of readmissions was 2 (range 0-40); overall rate was 3 hospitalizations/person-year

Volk ML et al. *Am J Gastroenterol* 2012;107:247-252.

Complications of Cirrhosis

Complications of Cirrhosis: Distinguish Portal Hypertension from Liver Insufficiency



General Management Guidelines - Cirrhosis

- Screen for hepatocellular carcinoma
  - Abdominal US (or CT/MRI) every 6 months
  - Alfa-fetoprotein (AFP) no longer recommended by AASLD but many experts still utilize
- Vaccinate for HAV, HBV, influenza (annual), Pneumovax; consider Zoster and HPV
- Avoid non-steroidals; acetaminophen preferred but in limited quantities (consider < 2-3gm/day)
- Cautious use of benzodiazepines and opioids; contraindicated in decompensated cirrhosis w/ HE
- Beware of raw shellfish (*Vibrio vulnificus*)
- Dietary considerations: adequate protein intake (1-1.2gm/kg/day), careful sodium intake (ideally <2gm/day)

General Management Guidelines - Varices

- Screening endoscopy:
  - All cirrhotic patients at diagnosis *(Class IIa, Level C)*
  - Every 2-3 years in Childs A with no or small varices
  - Annually in Childs B/C (or at time of decompensation)
- Non-selective beta-blocker (NSBB: propranolol, nadolol, carvedilol):
  - Childs B/C with small varices or Childs A with small varices with red signs *(Class IIa, Level C)*
  - Childs A with medium/large varices without red signs *(Class I, Level A)*
  - Childs A with small varices without red signs *(optional) (Class III, Level B)*
- NSBB *or* Esophageal Variceal Ligation (EVL, “banding”):
  - Medium/large varices in Childs B/C or Child A with red signs *(Class I, Level A)*
- EVL:
  - Acutely bleeding varices
  - Medium/large EV in Childs A, intolerant or non-compliant with NSBB *(Class I, Level A)*
  - All patients with previously bleeding varices (in combination with NSBB, secondary prophylaxis) *(Class I, Level A)*

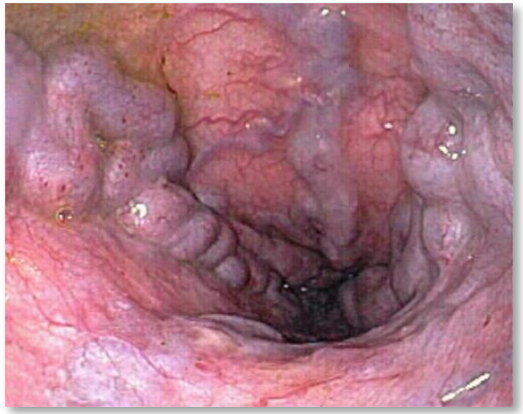
AASLD Guidelines, Updated 2009

Varices Increase in Diameter Progressively

No varices

Small varices

Lower risk of bleeding



Large varices

Higher risk of bleeding

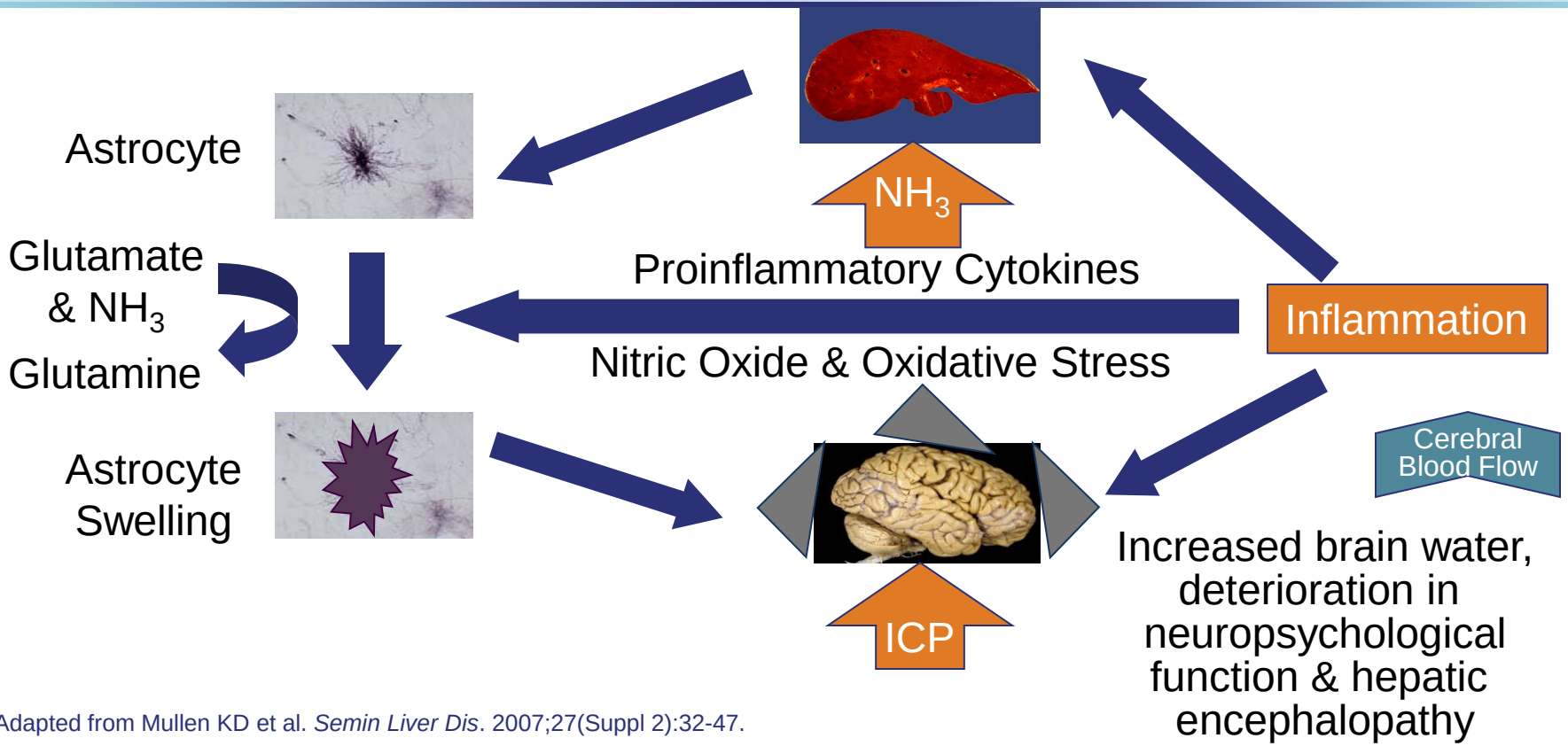
7-8%/year

7-8%/year

Merli et al. *J Hepatol* 2003;38:266

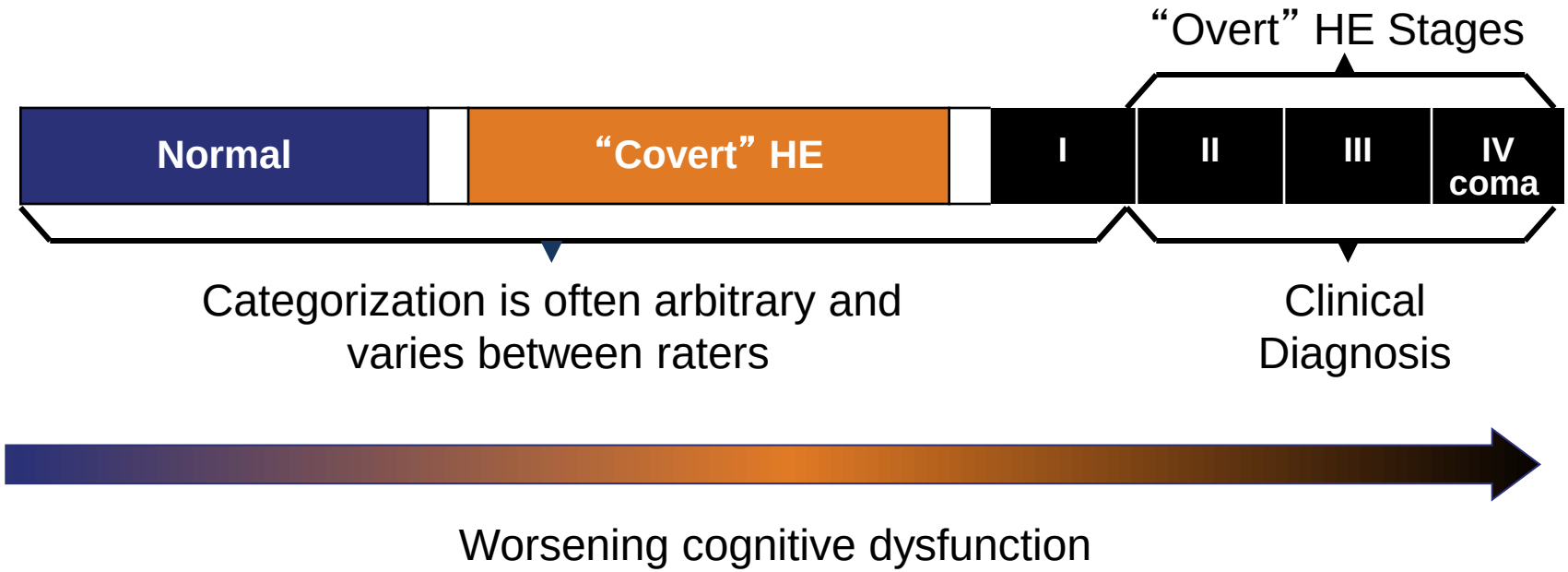
Hepatic Encephalopathy

Hepatic Encephalopathy: Pathophysiology



Adapted from Mullen KD et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47.

Characterization of HE Stages



Bajaj JS, et al. *Hepatology*. 2009;50:2014-2021.

New Guidelines for Hepatic Encephalopathy

AASLD PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver

Hendrik Vilstrup,[1] Piero Amodio,[2] Jasmohan Bajaj,[3,4] Juan Cordoba,[5†] Peter Ferenci,[6] Kevin D. Mullen,[7] Karin Weissenborn,[8] and Philip Wong[9]

Published online in *Hepatology* and *Journal of Hepatology* July 2014

Clinical Classification of HE

<table>
<tr><th>Type</th><th colspan="2">Grade</th><th>Time Course</th><th>Spontaeous or Precipitated</th></tr>
<tr><td rowspan="2">A</td><td>MHE</td><td rowspan="2">Covert</td><td rowspan="2">Episodic</td><td rowspan="3">Spontaeous</td></tr>
<tr><td>1</td></tr>
<tr><td rowspan="2">B</td><td>2</td><td rowspan="4">Overt</td><td rowspan="2">Recurrent</td></tr>
<tr><td>3</td><td rowspan="3">Precipitated (specify)</td></tr>
<tr><td rowspan="2">C</td><td>4</td><td rowspan="2">Persistent</td></tr>
</table>

Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

Role of Ammonia Testing in HE

- “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”

Specific Approach to Overt HE Treatment

- Four-pronged approach to management of HE (GRADE II-2, A, 1):
  - Initiation of care for patients with altered consciousness
  - Alternative causes of AMS should be sought and treated
  - Identification of precipitating factors and their correction
  - Commencement of empirical HE treatment

Management of Overt HE (OHE)

- Identify and treat precipitating factors for HE (GRADE II-2, A, 1)
  - Controlling precipitating factors is critical, because nearly 90% of patients can be treated with correction of the precipitating factor alone[1]
- Lactulose is the first choice for treatment of episodic OHE (GRADE II-1, B, 1)
- Rifaximin is an effective add-on therapy to lactulose for prevention of OHE recurrence (GRADE I, A, 1)
- Neomycin is an alternative treatment of OHE (GRADE II-1, B, 2)
- Metronidazole is an alternative treatment of OHE (GRADE II-3, B, 2)
- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)

1. Strauss E et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. *Hepatogastroenterology* 1992;39:542-545

Treatment Approach for Episodic OHE: Lactulose + Rifaximin vs. Lactulose

172 Cirrhotic Patients Screened

↓

120 Patients Enrolled

↓

Randomization

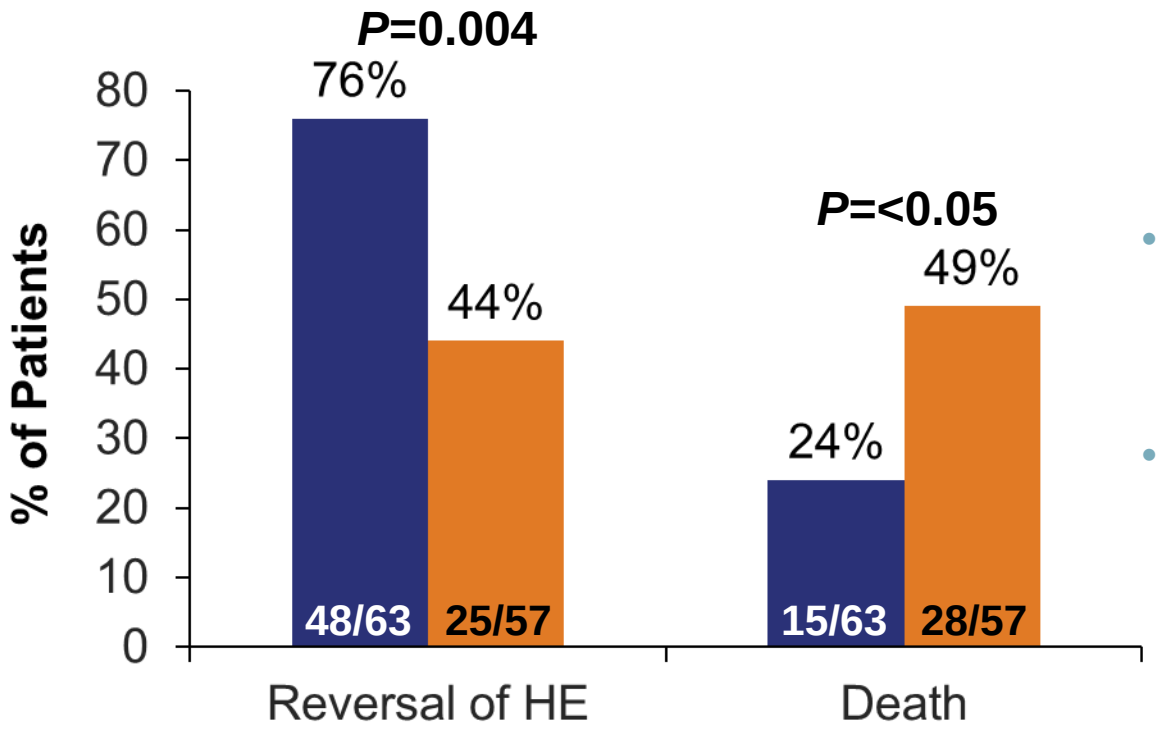
↙ ↘

Lactulose (30-60 mL TID) + Rifaximin (one 400 mg capsule TID) n=63 (10 grade 2, 20 grade 3, 33 grade 4)

Lactulose (30-60 mL TID) + Placebo (one sugar capsule TID) n=57 (12 grade 2, 20 grade 3, 25 grade 4)

Sharma BC et al. *Am J Gastroenterol* 2013;108:1458-1463.

Treatment Approach for Episodic OHE: Lactulose + Rifaximin vs. Lactulose



■ Lactulose + Rifaximin
■ Lactulose + Placebo

- Given via nasogastric tube until recovery of HE or a maximum of 10 days
- Hospital stay was shorter with Lactulose+ Rifaximin than with Lactulose + Pbo (5.8±3.4 vs. 8.2±4.6 days, *P*=0.001)

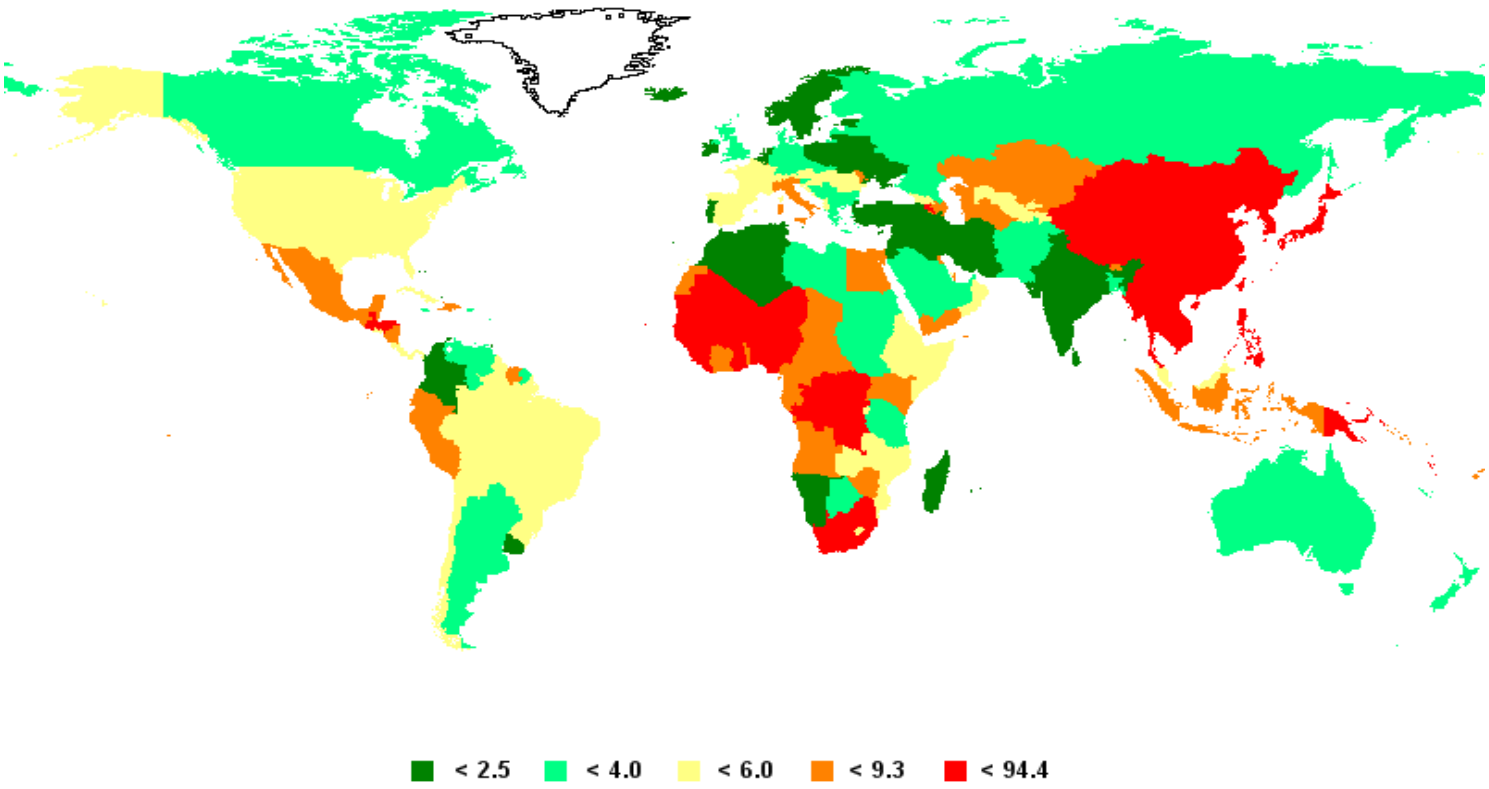
Sharma BC et al. *Am J Gastroenterol* 2013;108:1458-1463.

Summary

- Cirrhosis is increasing in prevalence in the U.S. and recognition with accurate diagnosis is critical for patient care
- Histologic or clinical diagnosis
- Be familiar with the various staging and prognostic tools: MELD, CTP, Baveno
  - Recognize the clinical importance of transition from compensated to decompensated cirrhosis
- HE is a frequent complication of cirrhosis
  - Familiarize yourself with new guidelines for its diagnosis, classification, and treatment

Hepatocellular Carcinoma

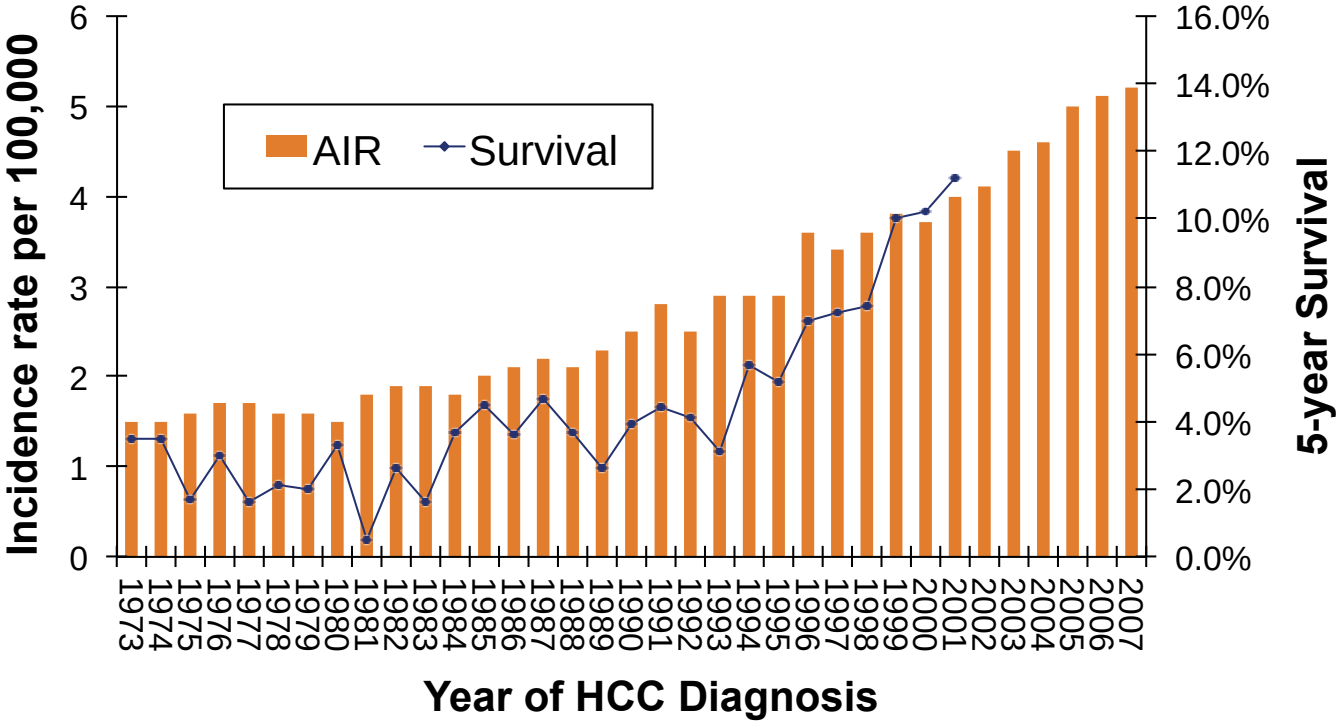
HCC: Age Standardized Incidence Rates 2005 (Men and Women)



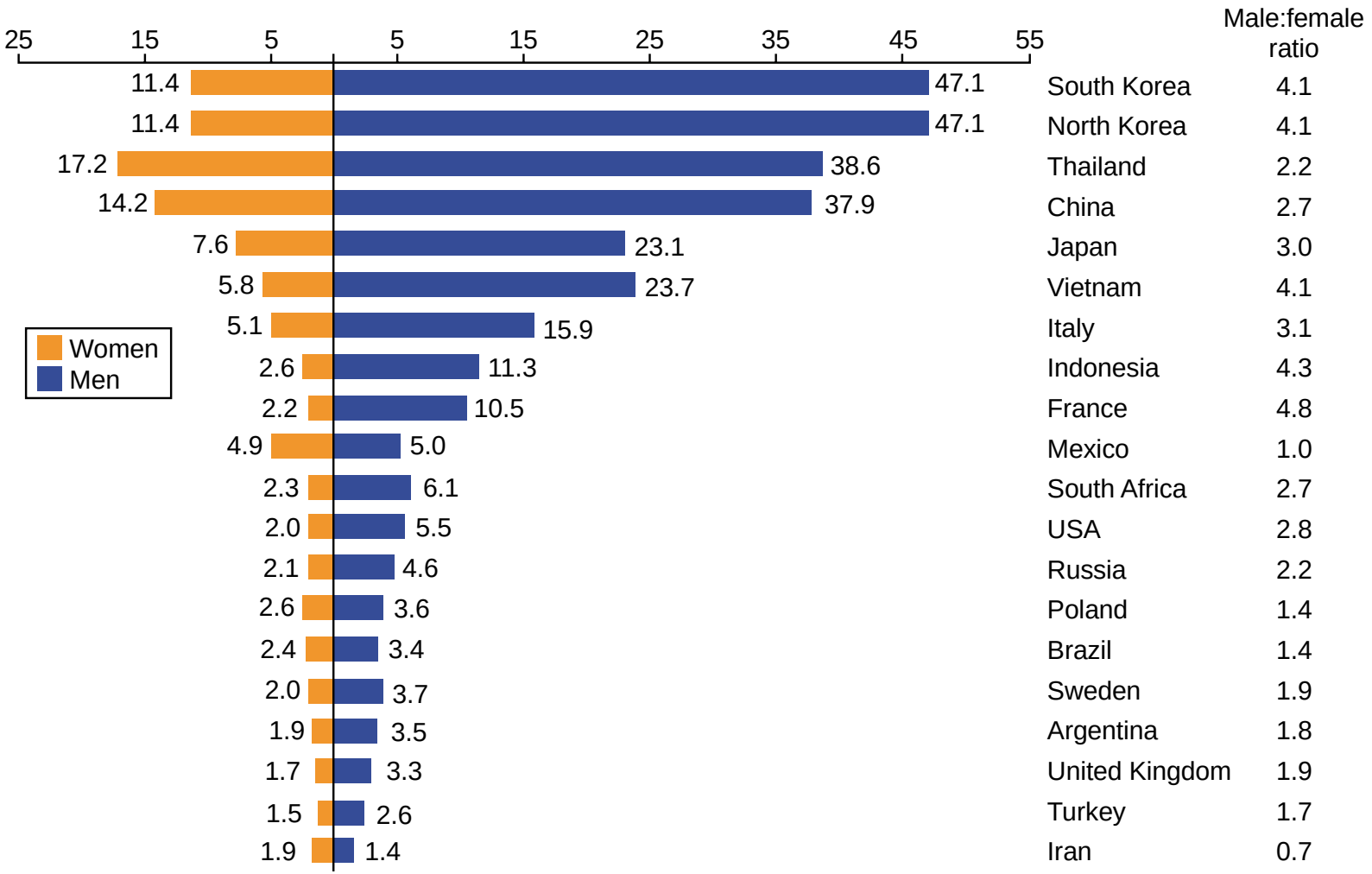
Global View of HCC

- Primary liver cancer increased from 437,408 cases in 1990 to 714,600 in 2002
- Incidence and mortality rates
  - Decreasing in areas of high and intermediate incidence, including China and Japan
  - Increasing in low-incidence areas, including the United States and Canada

The Incidence and 5-Year Survival of HCC in United States

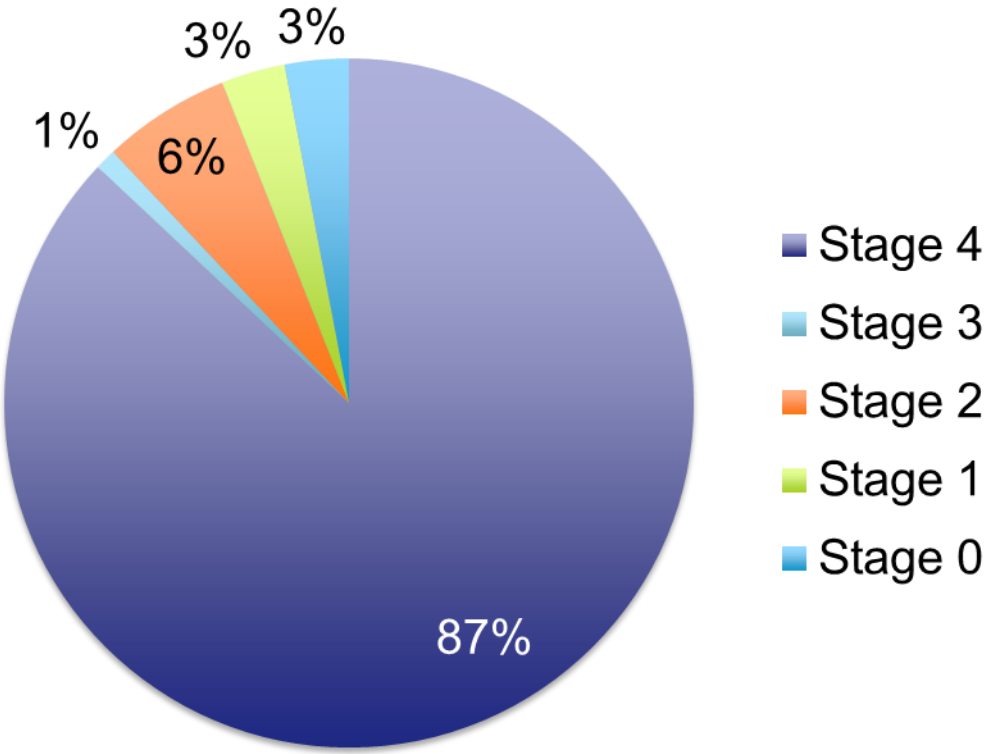


El-Serag HB. *N Engl J Med* 2011


25
15
5
5
15
25
35
45
55
Male:female ratio
Women
Men
11.4 47.1 South Korea 4.1
11.4 47.1 North Korea 4.1
17.2 38.6 Thailand 2.2
14.2 37.9 China 2.7
7.6 23.1 Japan 3.0
5.8 23.7 Vietnam 4.1
5.1 15.9 Italy 3.1
2.6 11.3 Indonesia 4.3
2.2 10.5 France 4.8
4.9 5.0 Mexico 1.0
2.3 6.1 South Africa 2.7
2.0 5.5 USA 2.8
2.1 4.6 Russia 2.2
2.6 3.6 Poland 1.4
2.4 3.4 Brazil 1.4
2.0 3.7 Sweden 1.9
1.9 3.5 Argentina 1.8
1.7 3.3 United Kingdom 1.9
1.5 2.6 Turkey 1.7
1.9 1.4 Iran 0.7

Liver Fibrosis and HCC

HCC can occur in non-cirrhotic livers, but most HBV patients with HCC have cirrhosis.



Yang JD, et al. *Clin Gastroenterol Hepatol*. 2011;9:64-70.

HCC in HCV

- Prevalence of HCV+ HCC (20-90%)
- Relative Risk of HCC
  - Compared to HCV- controls (25 fold)
- Absolute Risk of HCC
  - HCC in HCV (1 per 100 at 30 years)
  - HCC in HCV-related cirrhosis (3.5 per 100 [1-7])

Risk Factors for HCC in Chronic HCV: Host Factors

- Older age
- Duration of HCV infection
- Male sex
- Race
- Alcoholism
- Obesity
- Diabetes
- HBV co-infection
- HIV co-infection

HCV Viral Factors and Risk of HCC

- HCV Viremia (HCV RNA)
  - Any level (vs. none)
  - High level (vs. low)
    - Taiwan study show high HCC risk
    - US studies only as predictor of treatment response
- HCV Genotype
  - Possibly GT 1b
    - Meta analysis (1.78 increase in HCC odds)
  - GT 3

HCV Genotype 3 in the VA HCV Clinical Case Registry 2000-2009: Cirrhosis and HCC

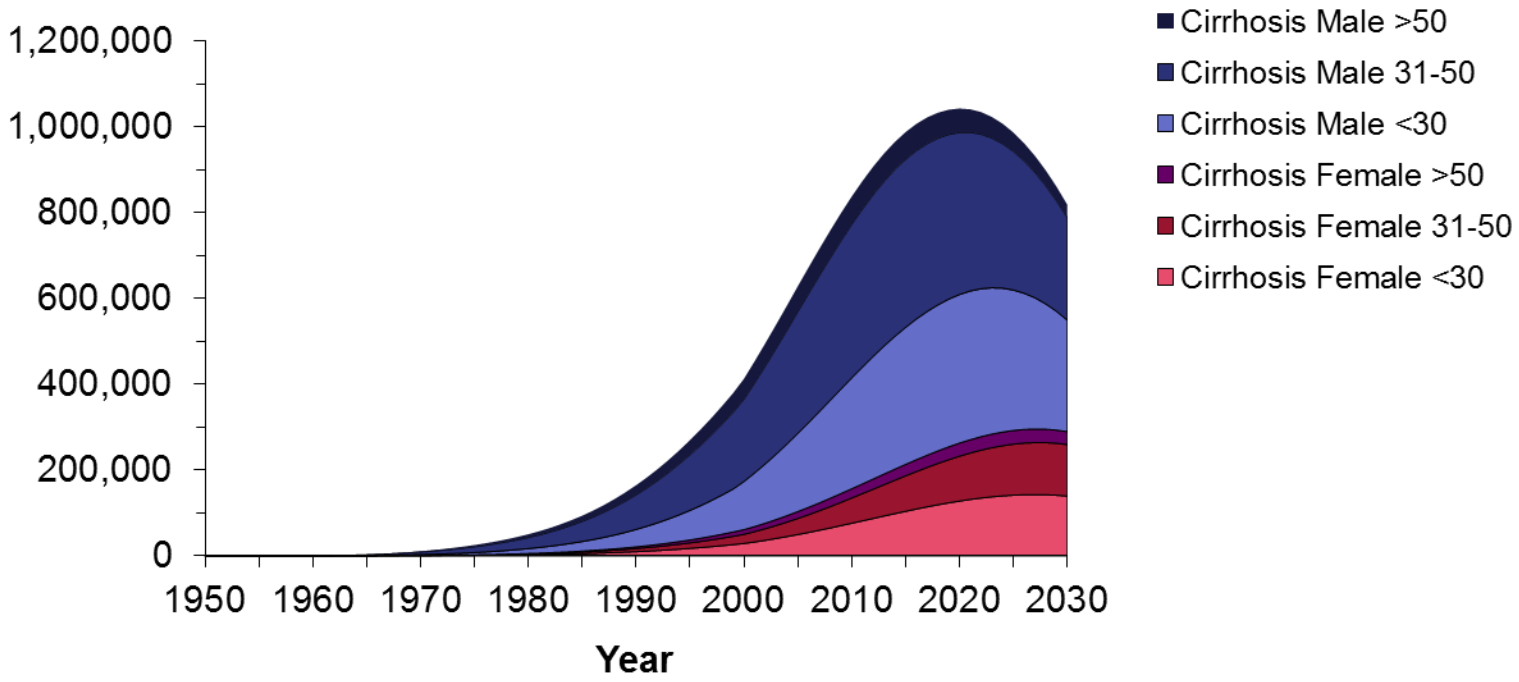
- 88,348 patients with genotype 1 (80%)
- 13,077 genotype 2 (12%)
- 8,337 genotype 3 (7.5%)
- Mean followup 5.4 years
- After adjustment for demographic, clinical and antiviral treatment factors, comparison between genotypes 3 and 1:

	Hazard Ratio	Confidence Interval
Cirrhosis	1.31	1.22.-1.39
HCC	1.80	1.61-2.03

Conclusion: Genotype 3 is associated with a significantly higher risk of cirrhosis and HCC vs genotype 1, independent of age, diabetes, BMI or antiviral treatment

Kanwal F et al, Hepatology 2014;60:98-105

HCV-related Cirrhosis by Cohort



Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings L *Gastroenterology* 2010

Determinants of HBV Disease Progression

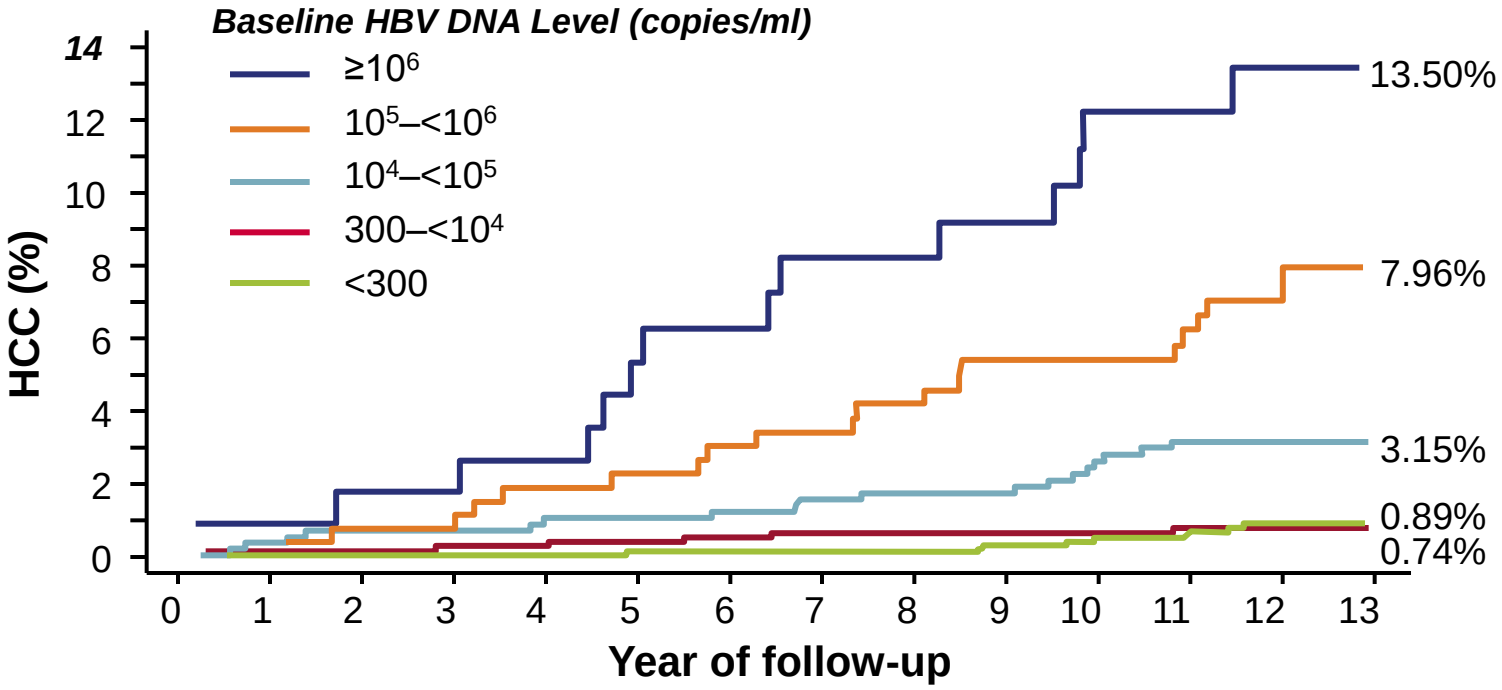
HBeAg-positive	HBeAg-negative
Prolonged interval before e-seroconversion	Persistent viral replication
Age > 40 Mildly, persistently abnormal ALT Genotype (C > B)	HBV-DNA Abnormal ALT Precore/BCP mutation
Male Alcohol Co-infection with HCV, HDV, HIV	

Yim HJ, et al. *Hepatology* 2006;43:S173-S181. Lai M, et al. *J Hepatol*. 2007;47:760-767.

Risk Factors for HCC in HBsAg-Positive Carriers

- Timing of HBV acquisition
- Older age
- Males > Females
- Cirrhosis > no cirrhosis
- Family History of HCC
- Heavy alcohol drinking
- Aflatoxin exposure
- HBeAg-positive carriers
- HBV genotype C
- HBV precore (decrease), core promoter (increase)
- Co-infection with HCV or HIV or HDV

Hepatitis B: Association Between Viral Load and Incidence of HCC



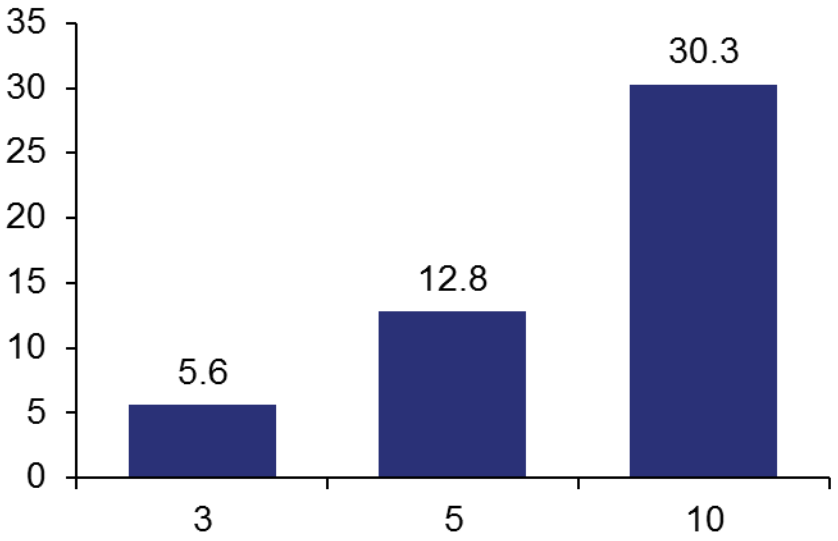
HBeAg negative, **normal ALT**, no liver cirrhosis at entry (n=2,925)

Chen CJ et al. *JAMA*. 2006;295:65–73

REACH-B Model

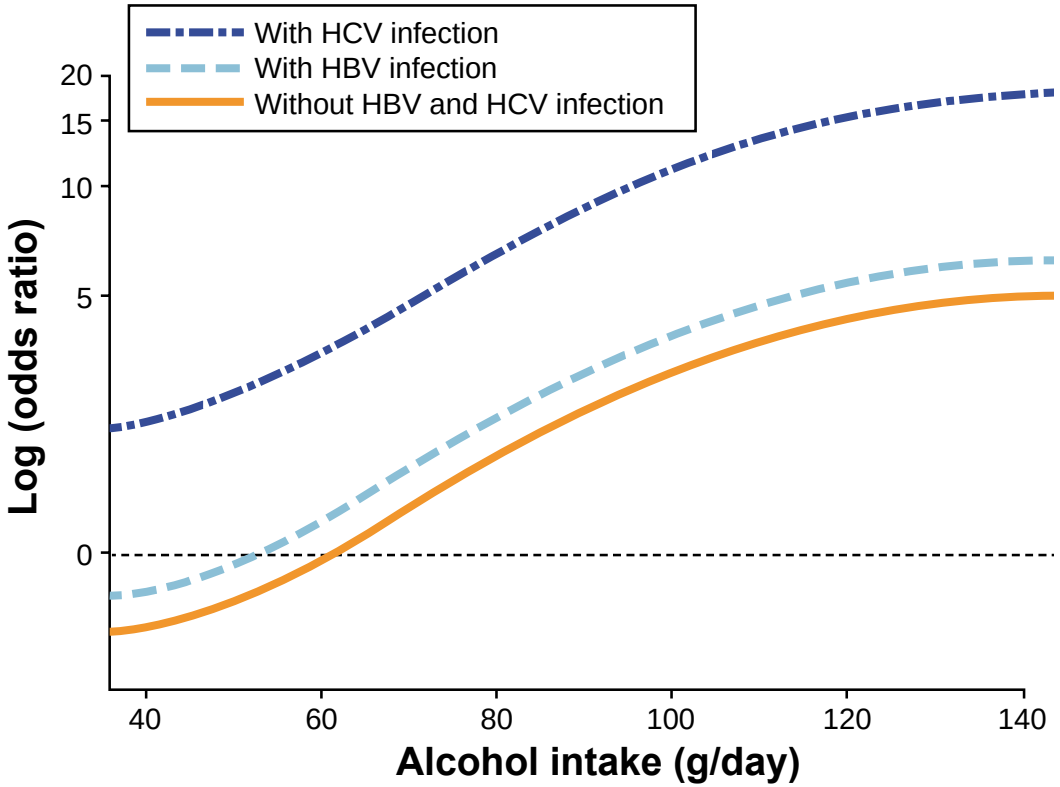
Variable	Data	Score
Sex	M/F	0-2
Age	Q 5 years over 30	0-6
ALT	<15 15-44 >45	0-2
HBeAg	+/-	0-2
HBV DNA	Und. ~10^4 ~10^5 ~10^6 >10^6	0-4

- 60 year-old HBeAg+ male ALT 47, HBV DNA 50,000
- REACH-B score=13



Yang HI. *Lancet Oncol* 2011; 12: 568–74

Alcohol and Viral Hepatitis

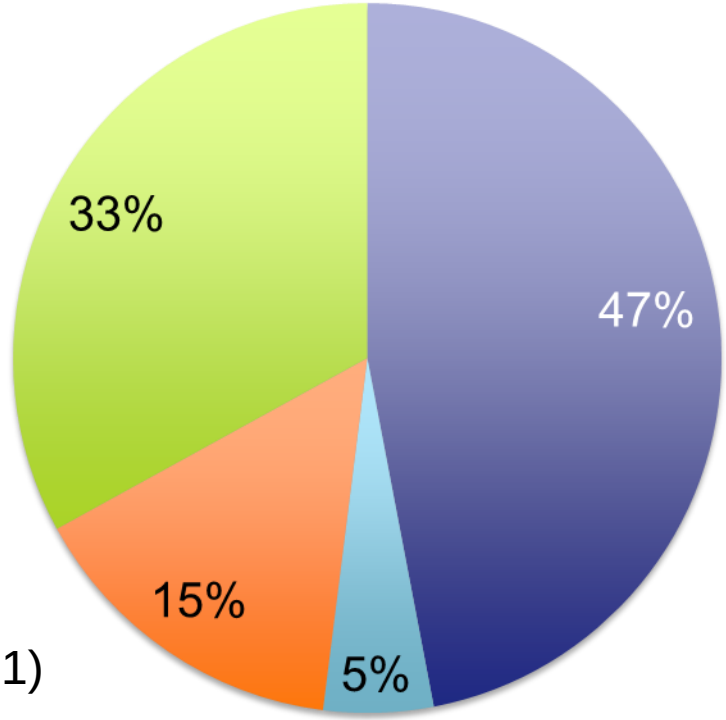


Gastroenterology 2012; 142:1264-1273.e1

Tobacco Smoking

- Smoking alone
  - Positive associations and no associations reported in different studies
- Smoking PLUS HBV and HCV infection
  - More than additive interaction between HBV infection and cigarette smoking
  - More than multiplicative interaction between HCV infection and cigarette smoking

HCV is the Dominant Risk Factor for HCC in the United States

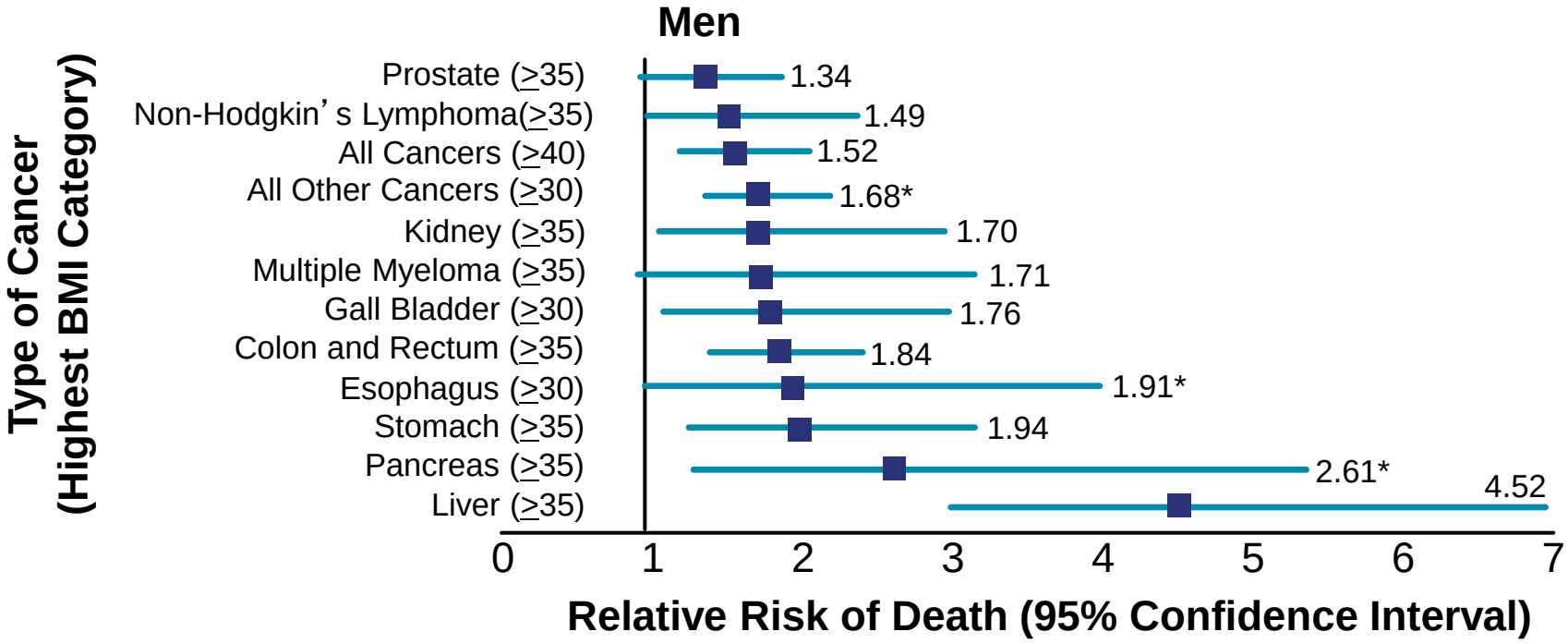


(N=691)

- HCV
- Both
- HBV
- Neither

- HBV most frequent in Asians
- HCV most frequent in whites and blacks

Mortality from Cancer in Obese US Men (n=900,053)

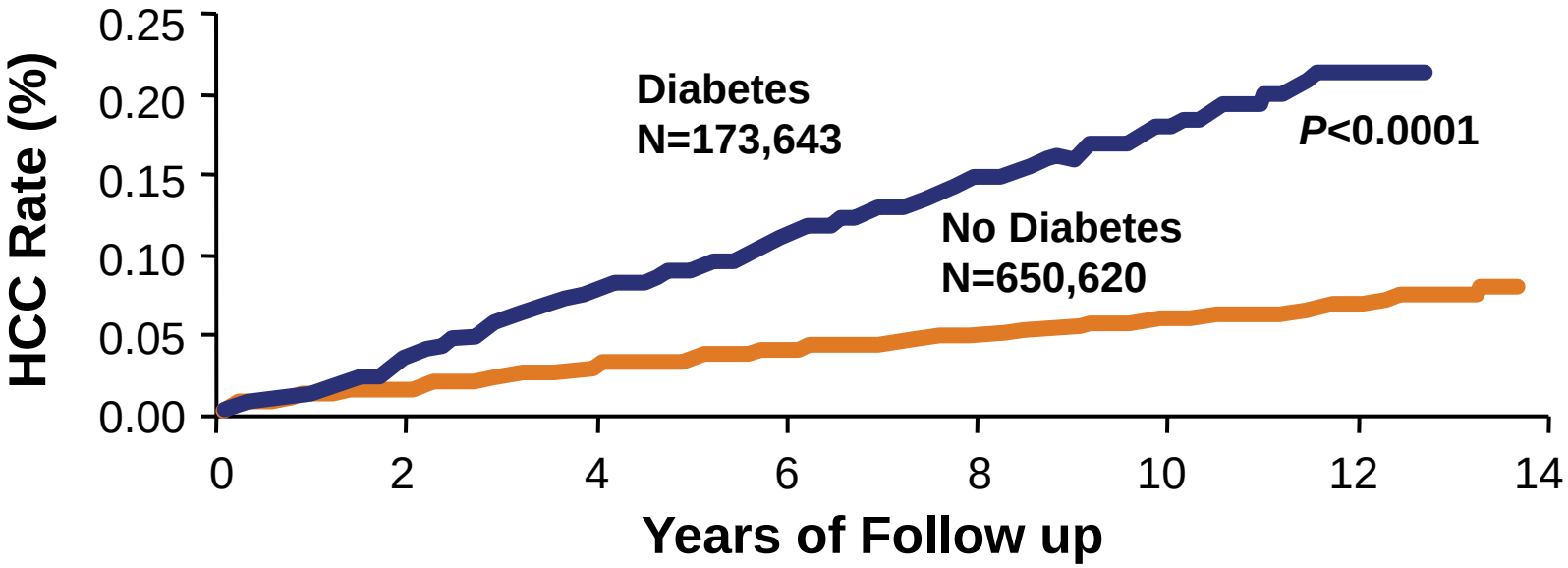


Calle, *NEJM* 2003

Obesity and Risk of HCC

- Systematic review of 10 cohort studies
  - Positive association between BMI and risk of HCC in 7 studies (relative risks ranging from 1.4 to 4.1)
  - No association in 2 studies
  - Inverse association in 1 study
- Limited by small number of cases with HCC, possibility of misclassification, and inconsistent adjustment for confounders

Diabetes Is Associated with a Two-fold Increase in Risk of HCC



El-Serag HB, et al, *Gastroenterology* 2004

NAFLD and Risk of HCC

- No evidence from population based data
- Possible increase in HCC risk in clinic based cohorts of NASH
  - ? Magnitude
  - ? Risk factors
- Consistent evidence from clinic based cohorts with NAFLD/NASH cirrhosis
  - Magnitude < HCV cirrhosis
  - Risk factors: obesity and diabetes

White D, Kanwal F, El-Serag. *Clin Gastro Hep* 2012

HCC in the Absence of Cirrhosis in United States Veterans

- ~13% of 1500 HCC cases developed in absence of cirrhosis
- These cases were more likely than HCC in cirrhosis to have
  - NAFLD or idiopathic compared to HCV or alcohol
  - Co-morbidities associated with metabolic syndrome
- While a small proportion, this poses logistical problems for HCC surveillance

El-Serag HB et al. DDW 2014

HCC Risk Factors:
Prevalence, Risk Estimates, Attributable Fraction?

	Prevalence in general population	Risk estimate of HCC	Current prevalence in HCC cases	Population attributable fraction
HBV	0.5-1%	20-25	10-15%	5-10%
HCV	1-2%	20-25	30-60%	20-25%
Alcoholic liver disease	10-15%	2-3	20-30%	20-30%
Metabolic syndrome	30-40%	1.5-2.5	20-50%	30-40%

Prevention of HCC

- HBV vaccination
- Treatment of viral hepatitis
- Coffee
- Statins
- Surveillance for HCC

HBV Vaccination and HCC: Taiwan Experience

ARTICLE

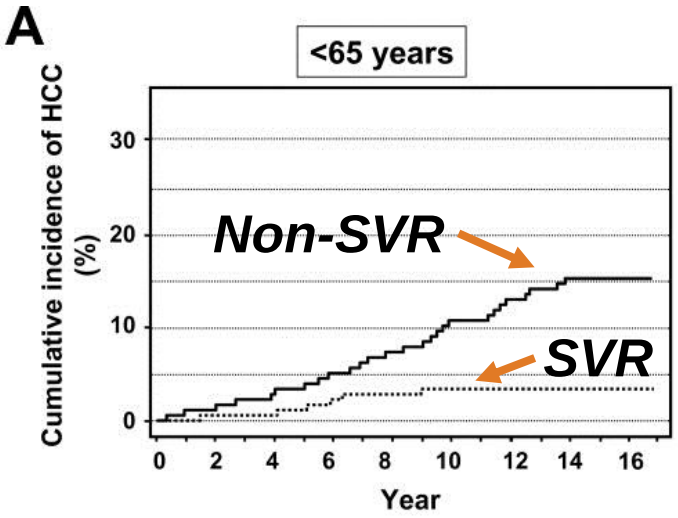
Decreased Incidence of Hepatocellular Carcinoma in Hepatitis B Vaccinees: A 20-Year Follow-up Study

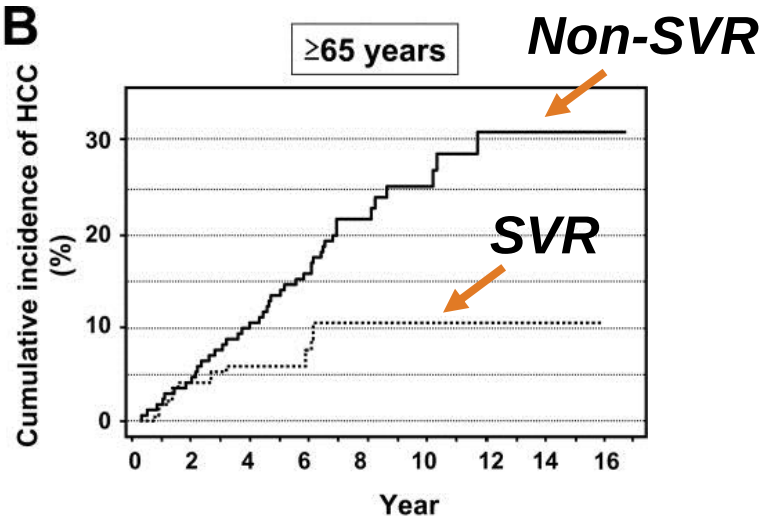
Mei-Hwei Chang, San-Lin You, Chien-Jen Chen, Chun-Jen Liu, Chuan-Mo Lee, Shi-Ming Lin, Heng-Cheng Chu, Tzee-Chung Wu, Sheng-Shun Yang, Hsu-Sung Kuo, Ding-Shinn Chen, the Taiwan Hepatoma Study Group

- HCC prevention extended from childhood to early adulthood
- Failures: incomplete vaccination, maternal HBsAg or HBeAg

J Natl Cancer Inst 2009;101:1348-1355

HCC and Hepatitis C Treatment



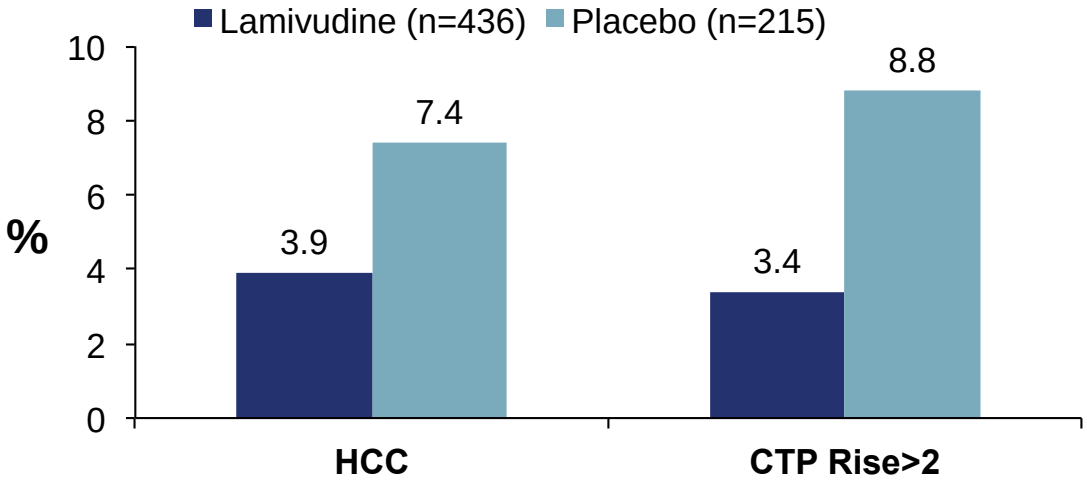


		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	6	12	12
	Patients at risk	565	376	164	56
	Cumulative incidence of HCC	0%	1.2%	3.3%	3.3%
Non SVR	Patients with HCC	0	33	72	85
	Patients at risk	980	723	345	141
	Cumulative incidence of HCC	0%	3.6%	10.9%	15.5%

		0	5 yrs.	10 yrs.	15 yrs.
SVR	Patients with HCC	0	7	10	10
	Patients at risk	121	67	21	5
	Cumulative incidence of HCC	0%	6.0%	11.0%	11.0%
Non SVR	Patients with HCC	0	46	61	64
	Patients at risk	376	179	43	25
	Cumulative incidence of HCC	0%	14.1%	25.5%	31.1%

Impact of HBV Treatment on HCC

- Randomized controlled trial comparing lamivudine versus placebo
  - Patients with advanced fibrosis or cirrhosis
  - HBV-DNA (>10^5 copies/mL) or HBeAg+
  - Study terminated prematurely by DSMB (median Tx=32.4 mo)



Liaw Y-F, et al. *N Engl J Med.* 2004;351:1521-1531.

Prevention of HCC (Antiviral Treatment)

Efficacy in
Clinical Trials and
Research Centers

≠

Effectiveness in
Community Practice

↓

Efficacy x Access x
Correct Diagnosis x Recommendation x
Acceptance x Adherence

El-Serag HB. et al. *Gastroenterology.* 2007;132:8-10.

Statins and HCC

Systematic Review

- Ten studies
  - 7 observational, 3 clinical trials
- Pooled OR: 0.63 (0.52-0.76)
  - Not in the 3 clinical trials
- Not other lipid lowering medications
- Unclear
  - Dose, duration, type

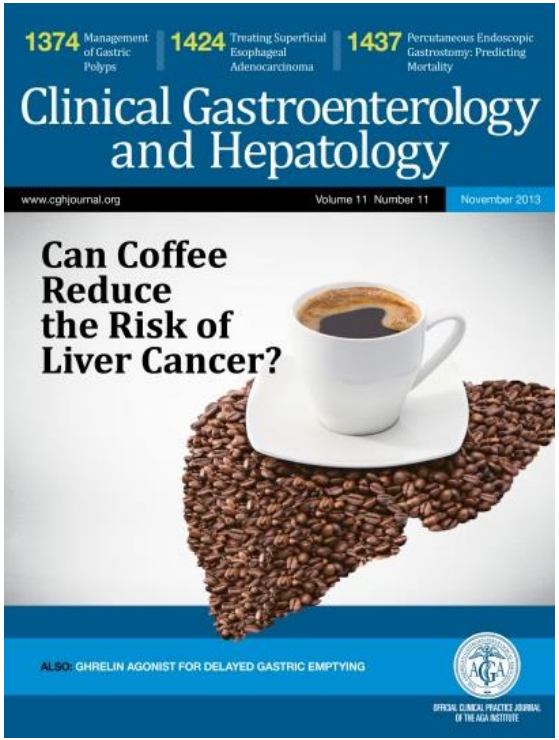
Metformin and Reduced Risk of HCC in Diabetic Patients: a Meta-analysis

- Seven studies:
  - Three cohort studies
  - Four case-control studies
- Significantly reduced risk of HCC in metformin users versus nonusers in diabetic patients
  - RR: 0.24, 95% CI 0.13–0.46, $p < 0.001$

Zhang H et al. *Scand J Gastroenetrol* 2013

Coffee and Hepatocellular Carcinoma

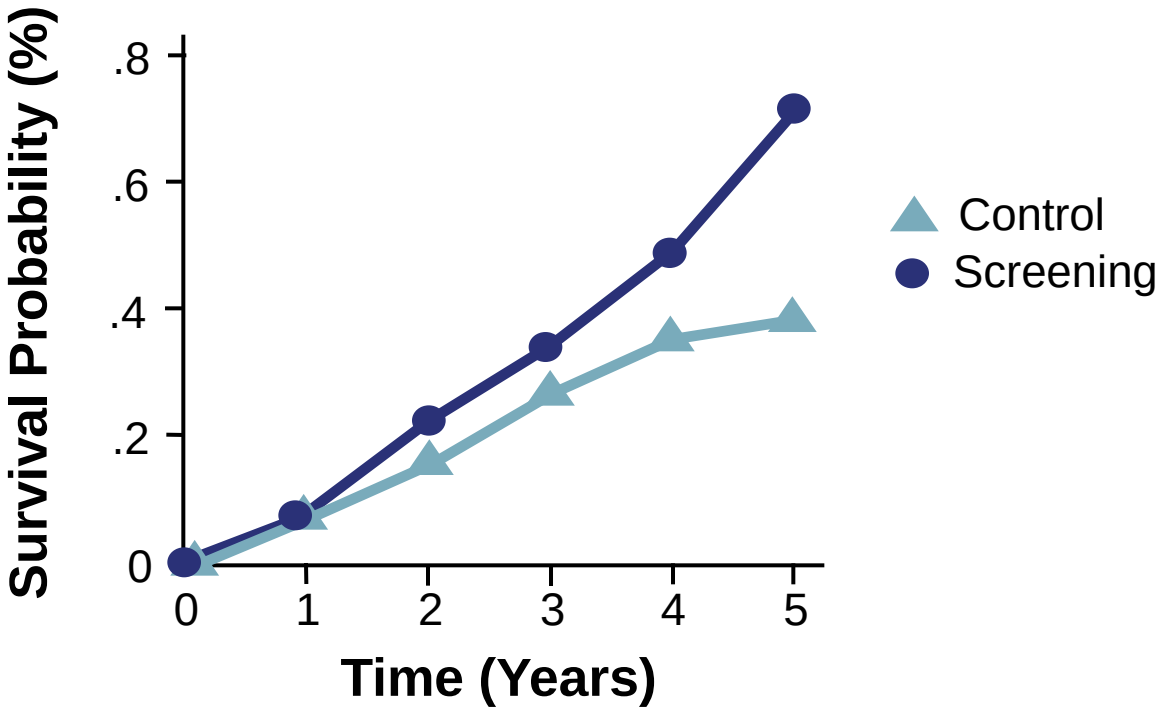
- Epidemiologic studies: coffee consumption is inversely related to
  - Serum liver enzyme activity
  - Liver cirrhosis
  - HCC
- For each additional 1 cup of coffee:
  - Case-control studies
    - (0.77, 0.72-0.83)
  - Cohort studies
    - (0.75, 0.65-0.85)



HCC Surveillance: Randomized Controlled Trials

- Cirrhosis (NONE)
- Hepatitis C infection (NONE)
- Hepatitis B infection carriers
  - China
  - Two trials
  - One showed benefit (Zhang et al. 2004)
  - One did not show benefit (Chen et al. 2003)

Surveillance for HCC Reduces Mortality:
A Randomized Controlled Trial of AFP+US q 6 months



Zhang BH, et al. *J Cancer Res Clin Oncol* 2004

Recommended Groups for HCC Surveillance

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG)(%/year)	Incidence of HCC (%/year)
Asian male hepatitis B carriers > age 40	0.2	0.4–0.6
Asian female hepatitis B carriers > age 50	0.2	0.3–0.6
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3–8
Hepatitis C cirrhosis	1.5	3–5

Sherman M. *Semin Liver Dis*. 2010;30(1):3-16.

Groups in Whom the Risk of HCC is Increased, but in Whom Efficacy of Surveillance Has **Not** Been Demonstrated

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG)(%/year)	Incidence of HCC (%/year)
Hepatitis B carriers <40 (males) or 50 (females)	0.2	<0.2
Hepatitis C and stage 3 fibrosis	1.5	<1.5
Noncirrhotic NAFLD	1.5	<1.5

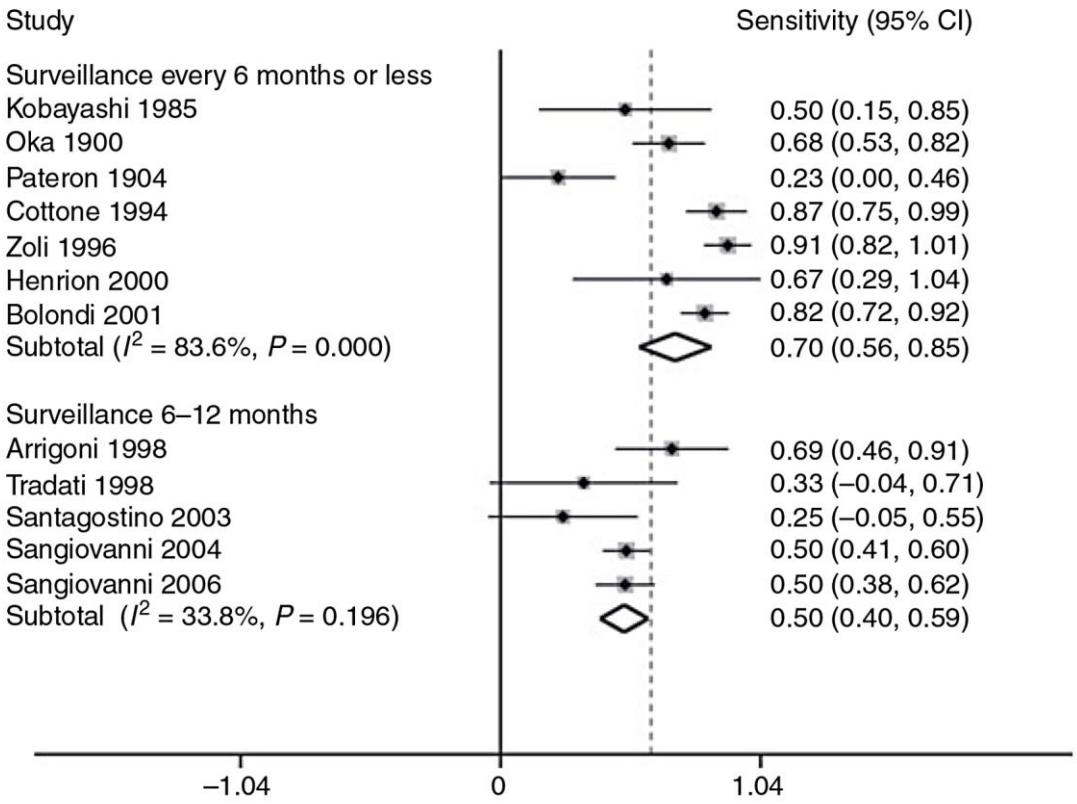
Sherman M. *Semin Liver Dis*. 2010;30(1):3-16.

AFP and Des-gamma-carboxy Prothrombin (DCP) in the Early Diagnosis of HCC

- 1031 patients randomized in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial
  - Nested case-control study of 39 HCC cases and 77 controls
- Testing within one month prior to HCC diagnosis
- DCP: sensitivity (74%) and specificity (86%) at a cutoff of 40 mAU/mL
- AFP: sensitivity (61%) and specificity (81%) at a cutoff of 20 ng/mL
- Combining both markers increased the sensitivity to 91% at month 0 but the specificity decreased to 74%

Lok, et al. *Gastroenterology* 2009

Ultrasound Surveillance in Early HCC: Systematic Review

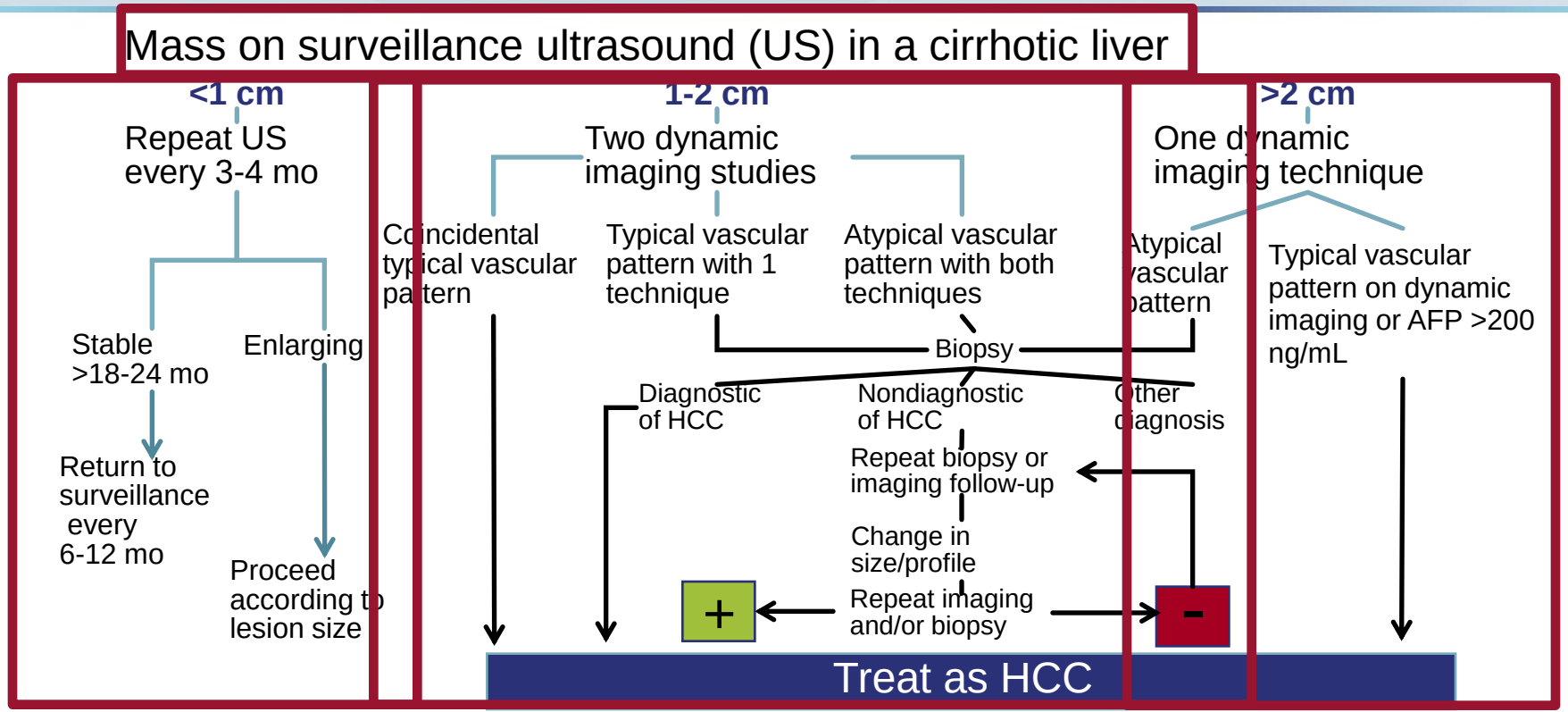


Singal A, et al. APT 20

HCC Surveillance Recommendations

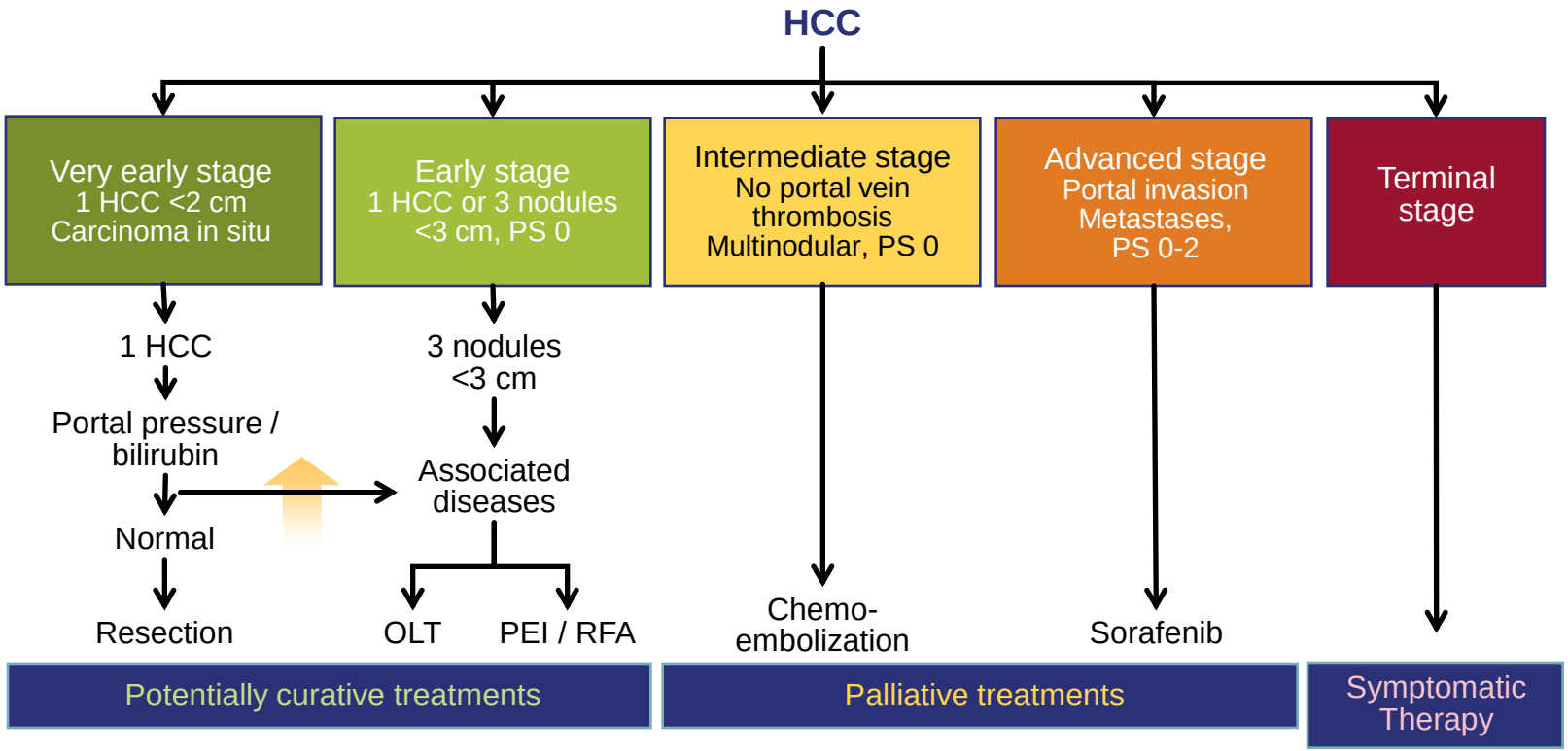
- The target population for surveillance are those with liver cirrhosis (and HBV-infected patients without cirrhosis in special circumstances)
- US and AFP are the recommended screening tests for HCC in patients at the highest risk
  - US is central
  - Not AFP alone
  - Premature to recommend dropping AFP

Diagnostic Criteria for HCC



Adapted from Bruix J and Sherman M. *Hepatology*. 2005; 42(5):1208

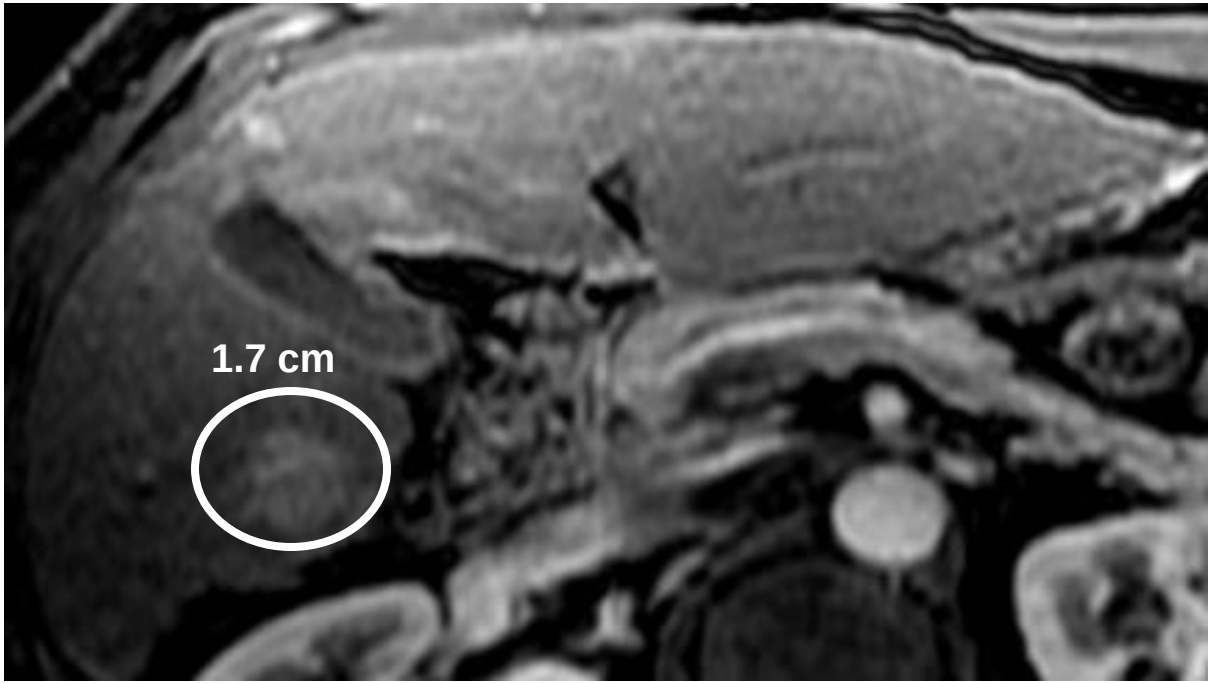
Hepatocellular Carcinoma: Treatment



El-Serag HB, et al. *Gastroenterology* 2008

Hepatocellular Carcinoma: Treatment

Very Early Stage HCC



Tumors < 2 cm with normal synthetic function

Hepatocellular Carcinoma: Treatment

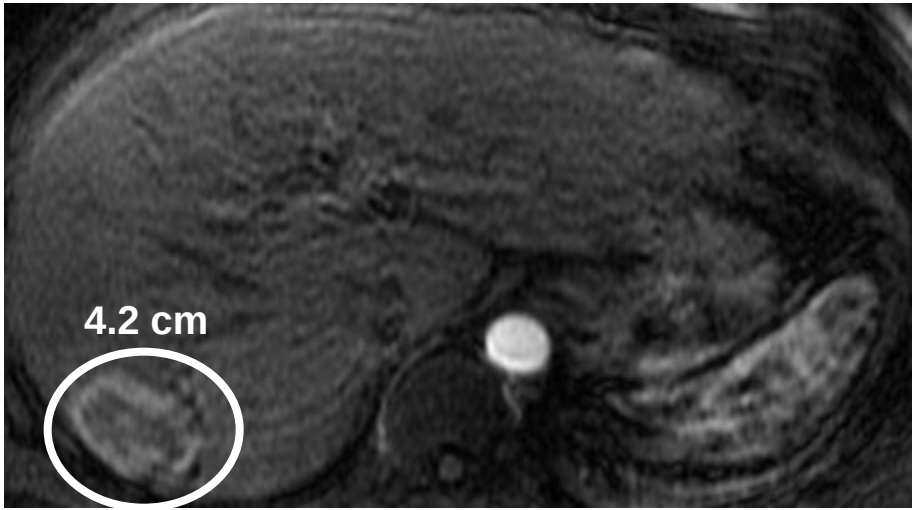
Randomized Trial of RFA versus Resection for Very Early HCC

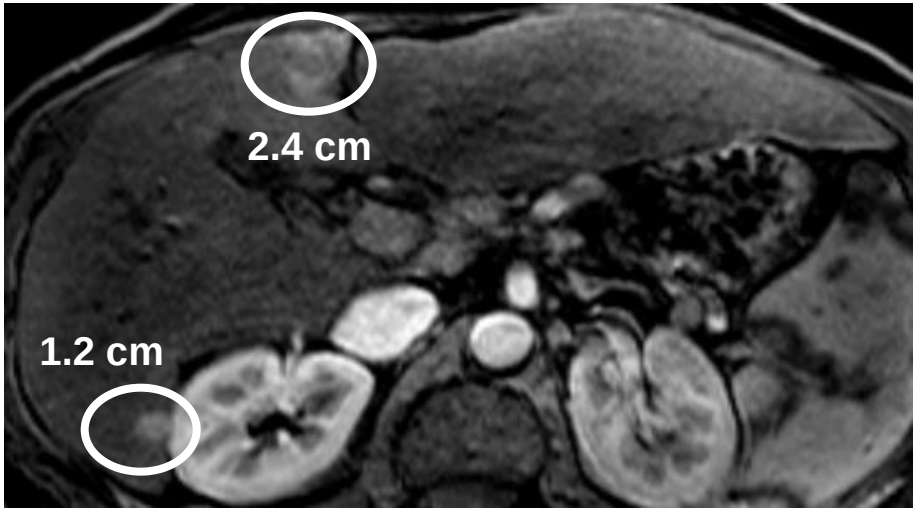
- Study Groups: RFA = 71; Resection =90
- No difference among groups in terms of liver function, performance status and tumor burden (all < 3 cm)

Chen MS, et al. *Ann Surgery* 2006; 243(3):321

Hepatocellular Carcinoma: Treatment

Early Stage HCC (Milan)





Single Tumor 2-5 cm or < 3 lesions each < 3 cm
with Child class A or B

Hepatocellular Carcinoma: Treatment

Transplantation (LT)

- Curative for HCC and chronic liver disease
- MELD exception points for HCC
- Live donor LT considered for HCC progression outside MILAN criteria
- UCSF criteria not implemented in current MELD exception allocation policy

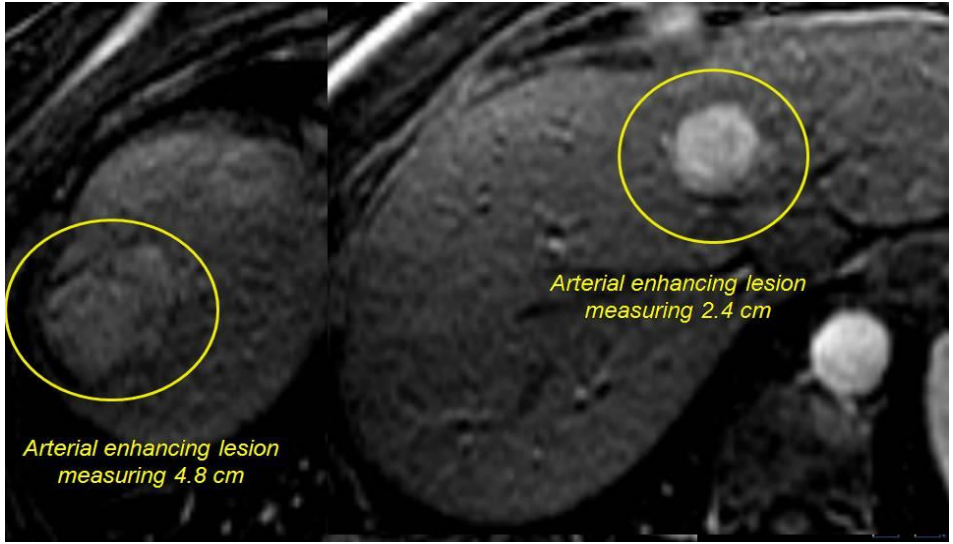
Survival

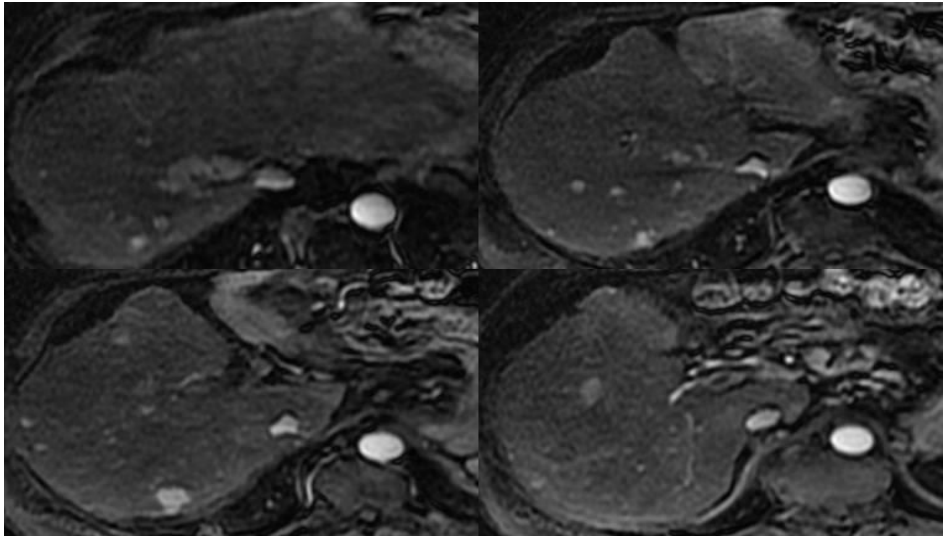
1 year	91%
2 year	75%
5 year Milan	>70%
5 year (extended)	~50%

Sala M,et al. *Liver Transpl* 2004;10(Suppl 2):S4-S9.
Mazzaferro V, et al. *N Engl J Med* 1996;334;693-699.
Shetty K, et al. *Liver Transpl* 2004;10:911-918.
Yao F, et al. *Hepatology* 2001;33:1394-1403.

Hepatocellular Carcinoma: Treatment

Intermediate Stage



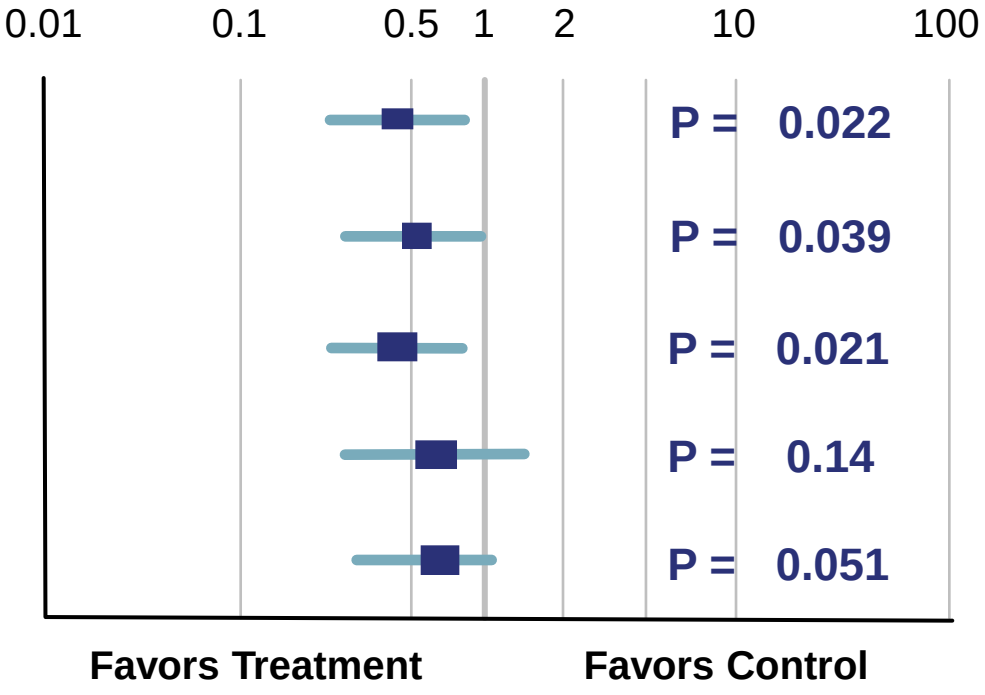


Single Tumor > 5 cm or multifocal tumor WITHOUT vascular Involvement; Child class A or B

Sensitivity Meta-Analysis of Core RCTs Reporting

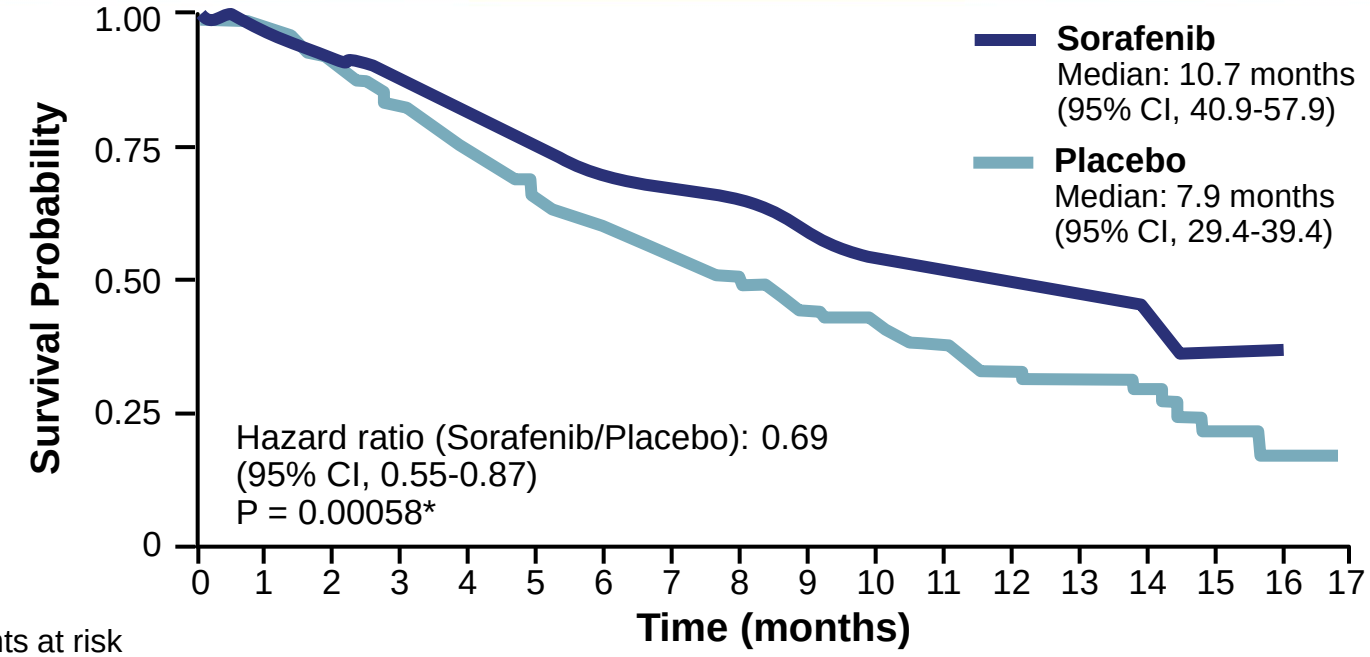
1 or 2-year Survival with Chemoembolization / Embolization: Various Treatment Comparisons

Comparison	Patients
Treatment vs no treatment 4 RCT	367
High quality trials 5 RCT	440
Chemoembolization vs control 4 RCT	323
Embolization vs control 3 RCT	215
Treatment vs control: 1 year survival 7 RCT	545



Adapted from Llovet JM, Bruix J. *Hepatology* 2003; 37:429

Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)



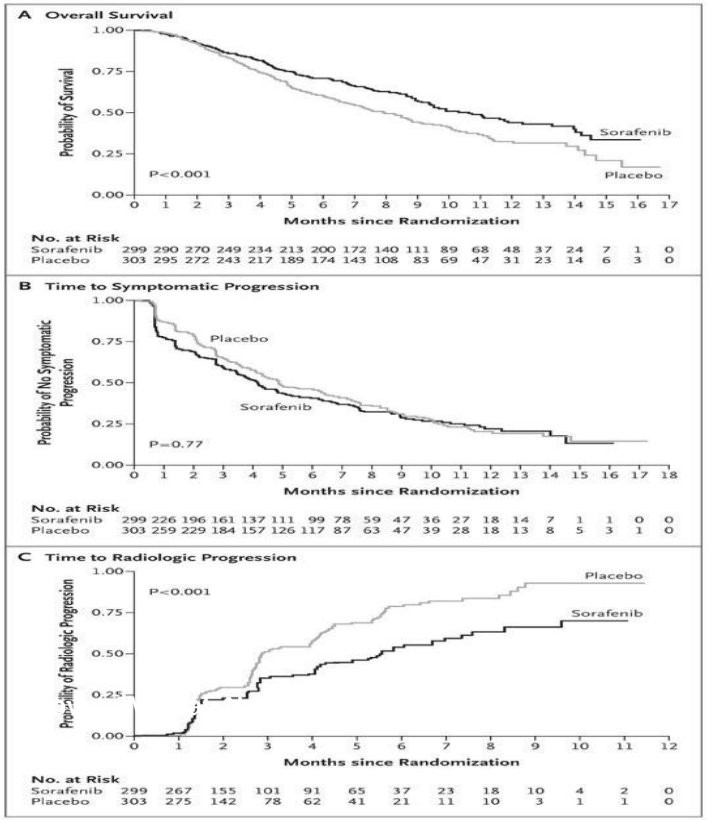
Patients at risk

Sorafenib:	299	274	241	205	161	108	67	38	12	0
Placebo:	303	276	224	179	126	78	47	25	7	2

*O'Brien-Fleming threshold for statistical significance was *P* = 0.0077; CI=confidence interval

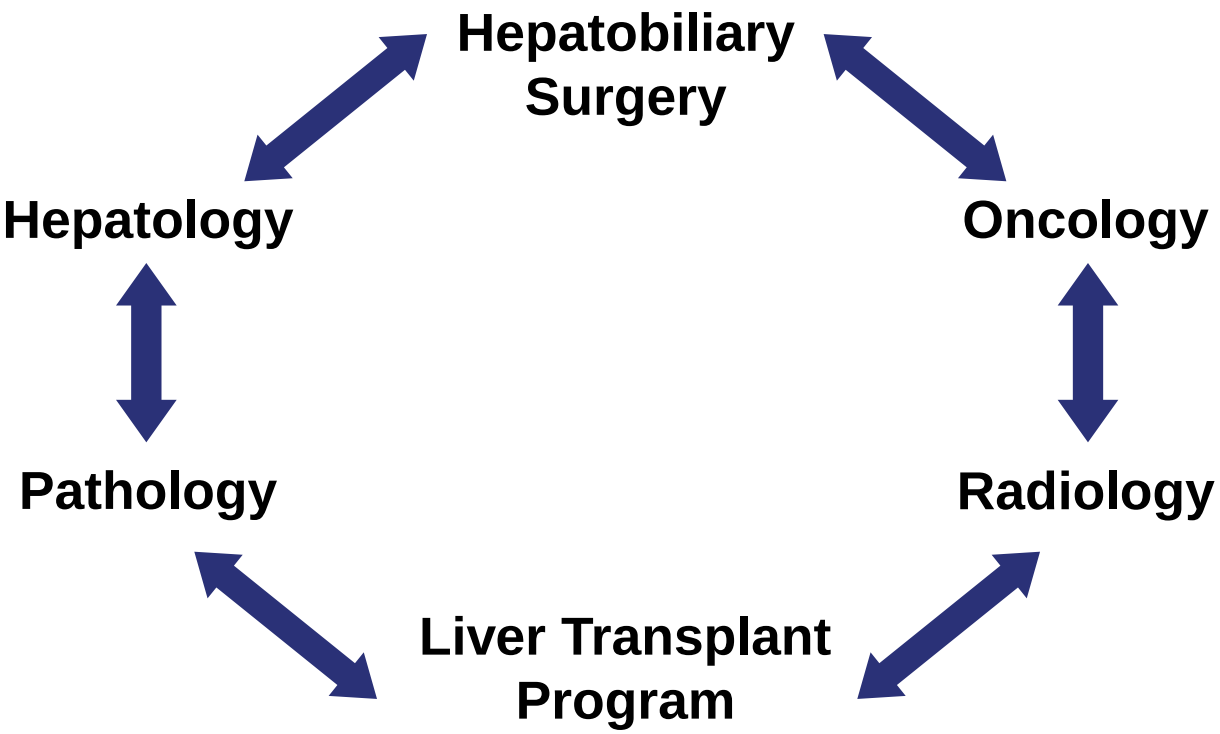
Llovet JM et al. *NEJM*. 2008; 359(4):378

Kaplan-Meier Analysis: Overall Survival, Time to Symptomatic Progression, Time to Radiologic Progression With Sorafenib



Llovet JM et al. N Engl J Med 2008;359:378-390

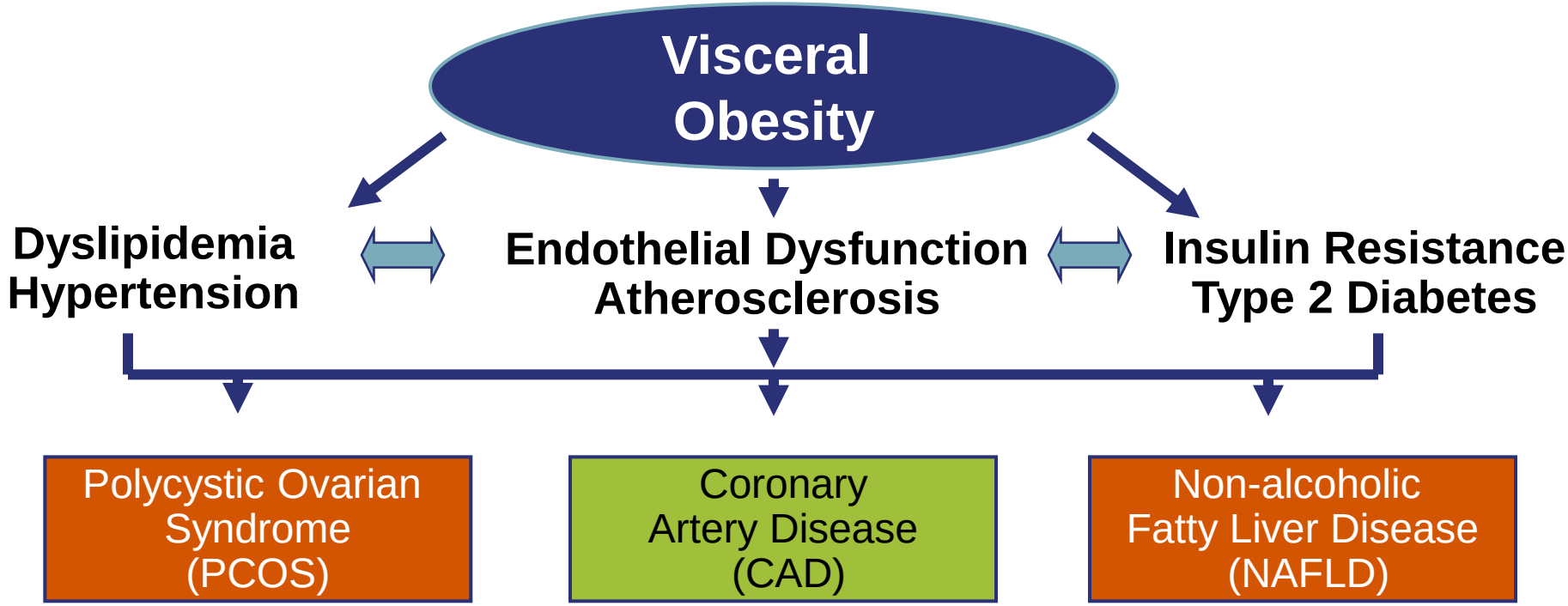
Management of Hepatocellular Carcinoma Requires a Multidisciplinary Approach



Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

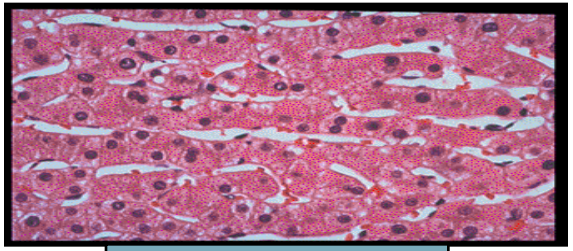
Diseases Associated with Visceral Obesity

NAFLD is Closely Associated with Visceral Obesity and Insulin Resistance

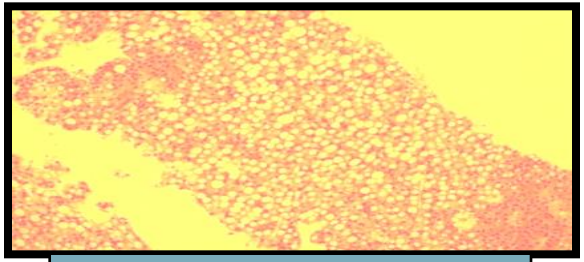


The Spectrum of NAFLD

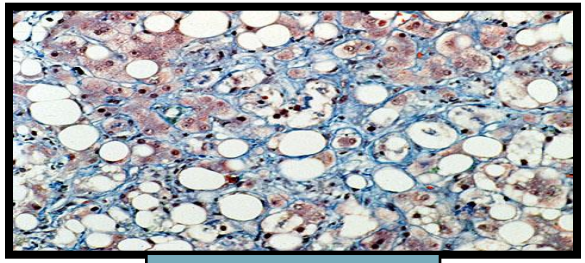
NAFLD Spectrum



Normal



Simple Steatosis or "NAFL"



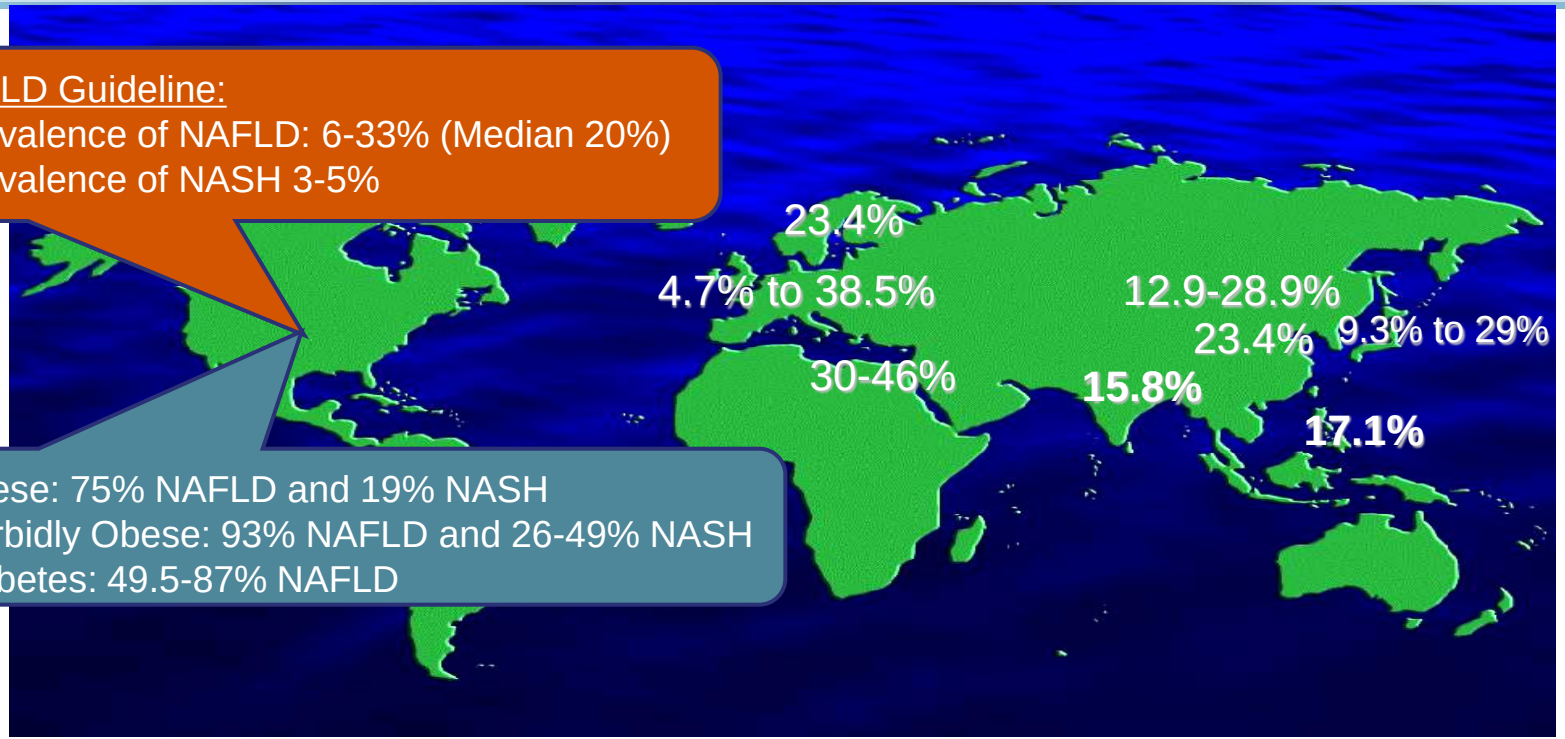
NASH

- Exclusion of liver diseases (HCV & ETOH)
- Requires specific pathologic criteria for NASH
- Important for prognosis

Ludwig 1980, Diehl 1988, Lee 1989, Powell 1990, Bacon 1994, Younossi 1997, Matteoni/Younossi 1999, Angulo 1999, Caldwell 1999, Ponawala 2000, Contos 2001, Ong/Younossi 2001, Bugianesi 2002, Ratziu 2002, Saddeh/Younossi 2002, Harrison 2003, Marchesini 2003, Younossi 2004, Gramlich/Younossi 2004, Fassio 2004, Sanyal 2004, Ong/Younossi 2005, Adams 2005, Ong/Younossi 2008, Mishra/Younossi 2008, Rafiq/Younossi 2010, Hossain/Younossi 2009, Kim/Younossi 2010, Stepanova/Younossi 2010, Hossain/Younossi 2010, Stepanova, Younossi 2012, Younossi 2012, Chalasani, Younossi 2012

Epidemiologic Impact of NAFLD

Worldwide Prevalence of NAFLD



AASLD Guideline:

- Prevalence of NAFLD: 6-33% (Median 20%)
- Prevalence of NASH 3-5%

- Obese: 75% NAFLD and 19% NASH
- Morbidly Obese: 93% NAFLD and 26-49% NASH
- Diabetes: 49.5-87% NAFLD

Hilden 1977, Ground 1982, Hultcrantz 1986, Nomura 1988, Nonomura 1992, El-Hassan 1992, Propst 1995, Lonardo 1997, Bellentani 2000, Clark 2001, Ruhl 2004, Browning 2004, Angelico 2005, Hamagushi 2005, Jimba 2005, Lin 2005, Fan 2005, Zelber 2006, Zhou 2007, Fan 2007, Targher 2007, Lazo 2008, Younossi 2011, Chalasani 2012

Prevalence of NAFLD in Children

- Using surrogate markers, prevalence of NAFLD in children is 2.6-17.3%
- Autopsy study from UCSD (N=742)
  - Prevalence: 9.6%, rates increasing with age
  - More common in boys
  - Highest rate in Hispanics

Schwimmer JB 2006, Argo C 2009

Prevalence of NAFLD in Large US Cohort

- Cohort: 11,613 NHANES-III participants
- NAFLD was defined as the presence of moderate-severe hepatic steatosis (by ultrasound), absence of excessive alcohol use and other chronic liver diseases
- Prevalence of overall NAFLD: 18.8% (N=2,185)

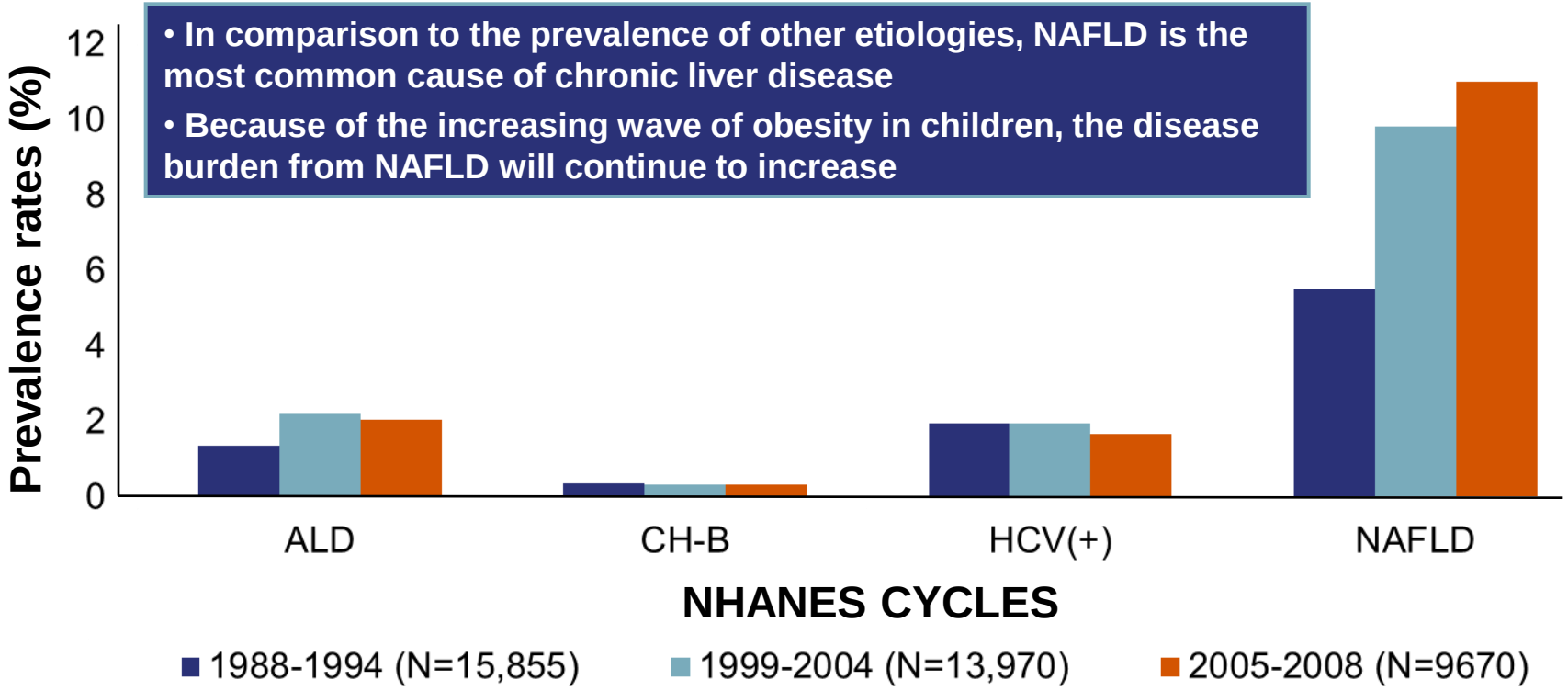
Younossi Z et al. *Medicine* Vol 91, Number 6, November 2012

Comparison of Lean and Non-Lean Patients with NAFLD

- NAFLD
  - 7% in lean population
  - 28% in overweight-obese population
- Both lean and non-lean NAFLD patients were older, more commonly of Hispanic ethnicity and had components of metabolic syndrome
- Data validates the independent association of NAFLD with components of metabolic syndrome and Hispanic ethnicity in a large population-based study

Younossi Z et al. *Medicine* Vol 91, Number 6, November 2012

Changes in the Prevalence of the Most Common Causes of Chronic Liver Diseases in the United States from 1988 to 2008 (N=39,750)

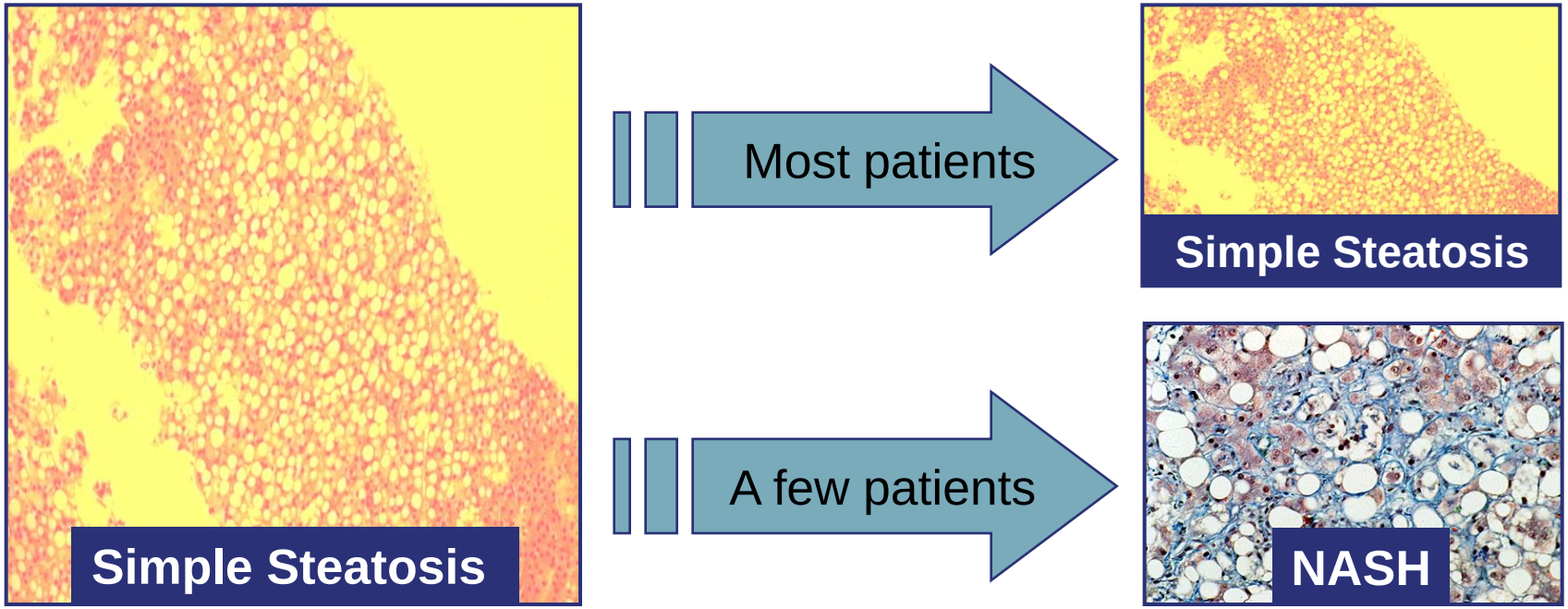


Younossi Z et al. *Clin Gastro and Hep* 2011

Natural History of the Spectrum of NAFLD

Natural History of NAFLD

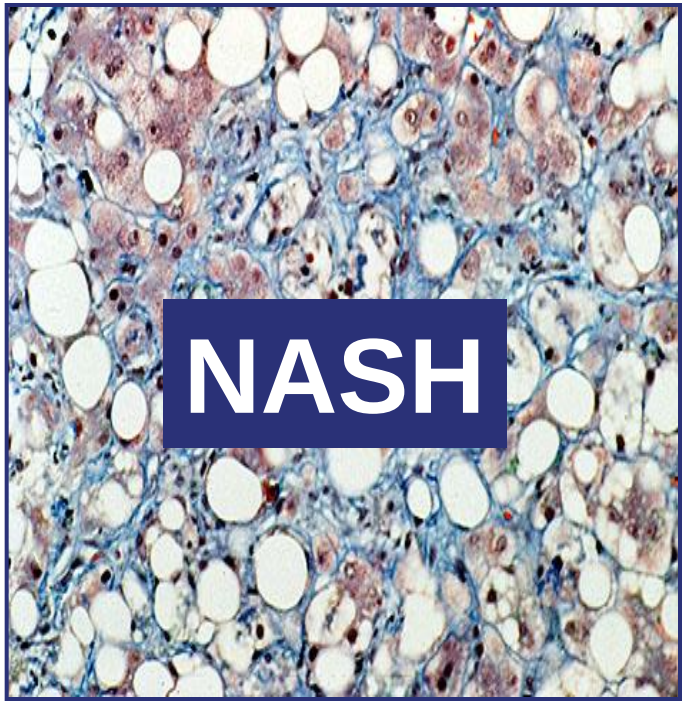
Simple Steatosis or NAFL



Teli M et al. *Hepatology* 1995, Matteoni C et al. *Gastroenterology* 1999, Ekstedt M et al. *Hepatology* 2006, Rafiq N et al. *Clin Gastro and Hep* 2009, Soderberg C *Hepatology* 2010

Natural History of NAFLD

Evidence to Support Progression of NASH



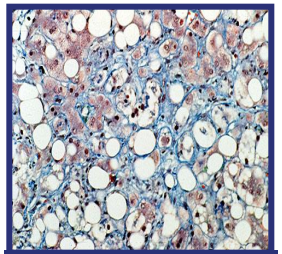
- Tertiary Medical Centers Data
- Sequential Biopsies Data
- Community Based Data
- Population Based Data
- Cryptogenic Cirrhosis Data
- HCC Data

NAFLD and HCC

- Several case reports and case series of well documented HCC in patients with NAFLD/NASH
- Two population-based cohort studies of NAFLD
  - One study suggested 0.3% over 6 years
- Three clinic based cohort studies of NAFLD or NASH (not restricted to cirrhosis)
  - Between 0 and 6% absolute risk of HCC in approximately 20 year follow up
  - Lower relative risk compared to alcohol or HCV

White D, Kanwal F, El-Serag H. *Clin Gastro Hepatol* 2012

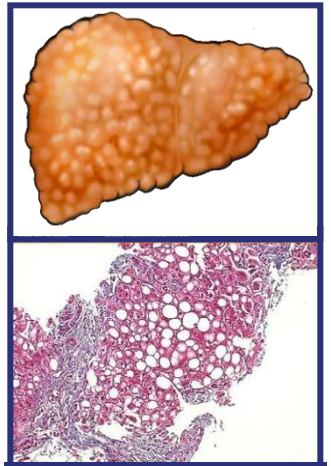
Summary of Outcomes of NASH



NASH

Overall

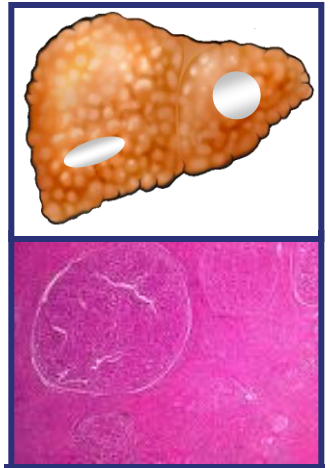
10-15%



Cirrhosis

Annual Incidence

2-3%



HCC

Ludwig 1980, Diehl 1988, Lee 1989, Powell 1990, Bacon 1994, Matteoni 1999, Angulo 1999, Caldwell 1999, Ponawala 2000, Contos 2001, Ong 2001, Bugianesi 2002, Ratziu 2002, Harrison 2003, Marchesini 2003, Younossi 2004, Fassio 2004, Sanyal 2004, Ong 2005, Adams 2005, Ong 2006, Rafiq 2008, Stepanova 2010, Younossi 2012

Can We Predict the Outcomes of Patients with NAFLD?

Predicting Outcomes of NAFLD

Liver Related Mortality

- 209 NAFLD patients with liver biopsy slides, clinical data and mortality data were included
- Median follow up = 146 months (max 342 months)
- During follow-up, 31% of patients died with 9% dying of LRM
- Regardless of the pathologic criteria used, NASH patients had higher LRM than non-NASH NAFLD
  - (13.0% vs. 1.3% for Original NAFLD NASH, p = 0.0047)

Younossi Z et al *Hepatology* 2011

Association of Pathologic Features with LRM

Univariate survival analyses [HR (95% CI) , p-value]

- Portal inflammation (grade ≥ 2) [6.68 (2.20-20.3), p<0.001]
- Ballooning degeneration (grade ≥ 2) [5.32 (1.89-14.9), p=0.001]
- Mallory-Denk bodies (grade ≥ 2) [4.21 (1.66-10.7), p=0.002]
- Portal fibrosis (grade > 2) [14.1 (5.47-36.5), p<0.001]
- Pericellular fibrosis (grade > 2) [4.86 (1.73-13.7), p=0.003]

Younossi Z et al *Hepatology* 2011

Association of Pathologic Features with LRM

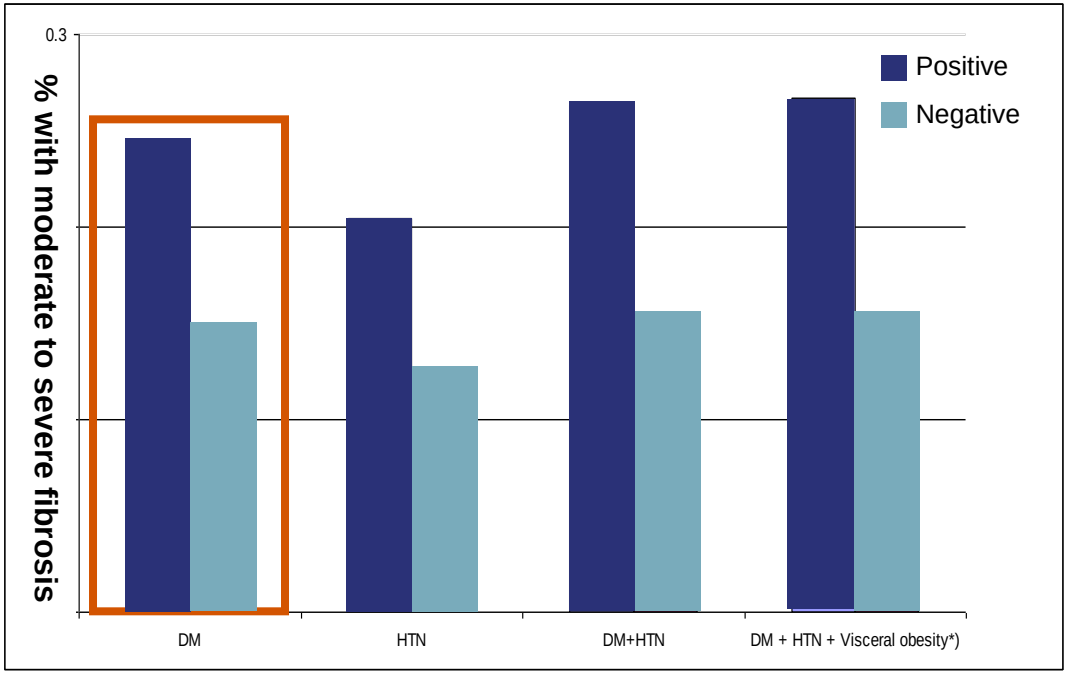
- On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM

Younossi Z et al *Hepatology* 2011

Predicting Advanced Fibrosis

NAFLD Patients With Components of MS are at Highest Risk for Advanced Fibrosis

- NAFLD with liver biopsy (N=432)
- In multivariate analysis, elevated **AST and ALT, presence of diabetes mellitus**, male gender and Caucasian ethnicity were associated with moderate to severe fibrosis (p-value<0.0001)



Hossain N, et al. *Gastro and Hepatology* 2009

Predicting Mortality

Long-term Outcomes of Diabetics with NAFLD

- NAFLD & DM (n=44) vs. NAFLD alone (n=88)
- Patients with NAFLD and DM have*:
  - Higher rate of cirrhosis (25% vs. 10.2%, p=0.04)
  - Higher liver-related mortality (RR=22.83, p=0.003)
  - Higher mortality (RR=3.3, p=0.002)

*Average follow up = 10 years

Younossi et al. *Clin Gastro and Hepatology* 2004

Predicting Outcomes of NAFLD

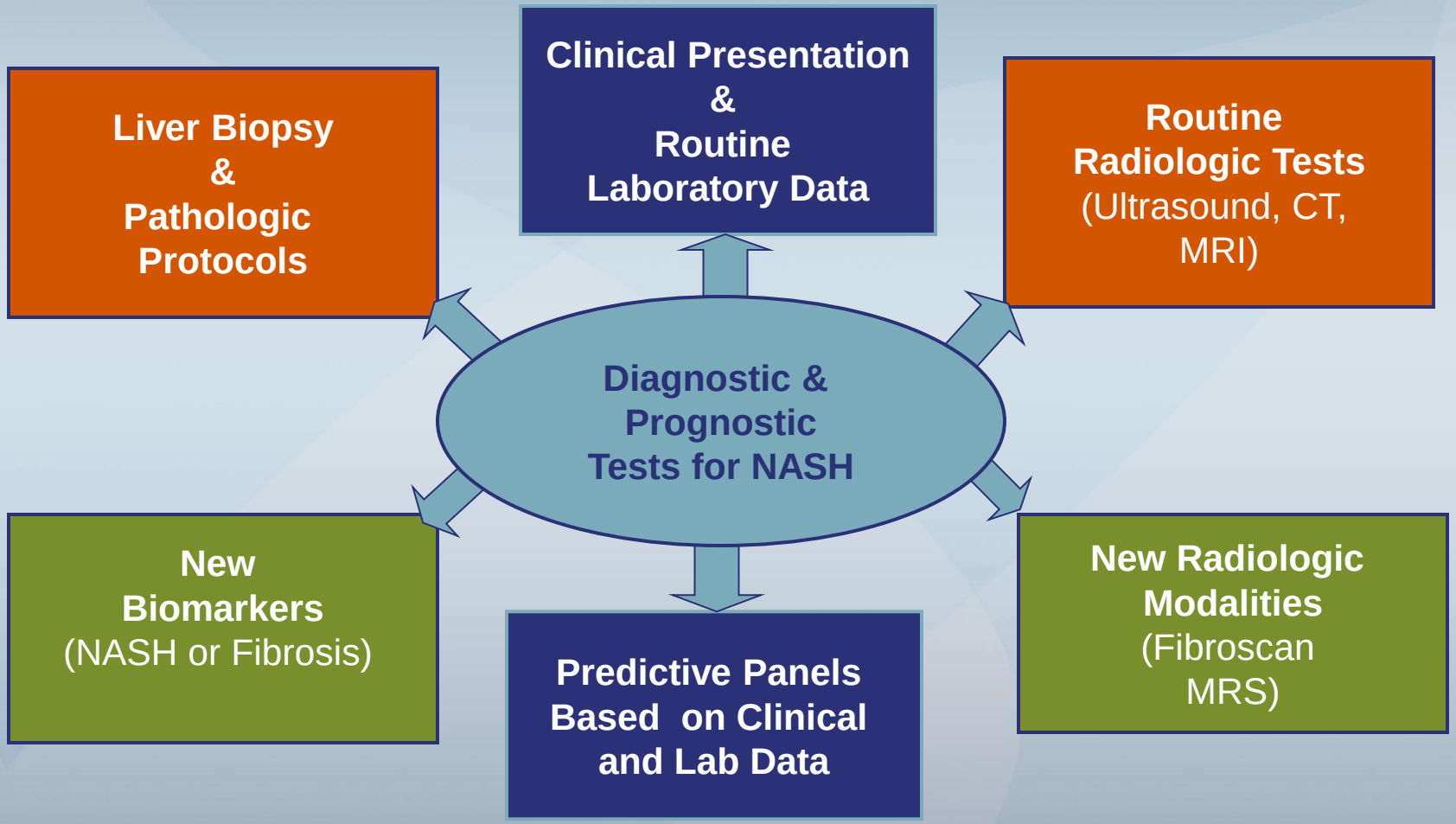
Liver Related Mortality

- NHANES III-NDI Linked Mortality Files (N=15,866)
  - NAFLD (N=991) and No Liver Disease (13,004)
- Over 160 months, 3,662 deaths (177 NAFLD)
- **Independent risks for liver-related mortality in NAFLD:**
  - **IR:** AHR = 53.55 (9.22 - 344.29), $p < 0.0001$
  - **Obesity:** AHR = 11.19 (2.43 - 51.56), $p = 0.003$
  - **Metabolic syndrome:** AHR = 12.08 (1.10 - 132.22), $p = 0.042$
  - Older age: AHR = 1.10 (1.08 - 1.12), $p = 0.020$
  - Male gender: AHR = 9.53 (1.36 - 66.55), $p = 0.024$

Stepanova M, Rafiq N, Younossi Z *Gut* 2010

Predictors of Advanced Fibrosis or Liver-related Mortality

Variables	Angulo	Marchesini	Ratziu	Dixon	Ong	Younossi	Ekstedt	Westin
Age	X		X			X	X	
Ethnicity								X
AST/ALT	X							
ALT or AST			X	X	X		X	
BMI	X		X				X	
WHR					X			
DM	X					X		
IR				X			X	
HTN				X				
MS		X						


Clinical Presentation
&
Routine
Laboratory Data
Liver Biopsy
&
Pathologic
Protocols
Routine
Radiologic Tests
(Ultrasound, CT,
MRI)
Diagnostic &
Prognostic
Tests for NASH
New
Biomarkers
(NASH or Fibrosis)
New Radiologic
Modalities
(Fibroscan
MRS)
Predictive Panels
Based on Clinical
and Lab Data

Radiologic Assessment of Non-alcoholic Fatty Liver Disease

- **Liver Stiffness:** Ultrasound elastography or MR elastography (problems with reproducibility and inability to discriminate lower stages of fibrosis and no validity for longitudinal studies.
- US elastography can fail in visceral obesity
- **Liver Fat Content:** MRI/MRS proton density fat fraction

Study	Yr	N	Mod	Comment
Mathiesen	2002	165	US	• Echogenicity could not detect fibrosis
Saadeh	2002	25	US, CT, MRI	• Excellent to predict>30% steatosis • Unable to diagnose NASH and stage fibrosis
Brunt	2004	30	CT	• Hepatic fat content (L/S) not associated with

NAFLD Guideline Recommendations

Non-invasive Assessment

- NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis (Strength - 1, Evidence - B)
- Although serum/plasma CK18 is a promising biomarker for identifying steatohepatitis, it is premature to recommend in routine clinical practice (Strength - 1, Evidence - B)

Pathologic Protocols Used in NASH

Ludwig, 1980 **(Original)**	• Steatosis, lobular inflammation, necrosis and Mallory bodies in zone 3, mild portal and periportal inflammation		
Younossi, 1999 **(NAFLD Subtypes)**	• Steatosis, ballooning degeneration	• Steatosis, ballooning with either Mallory's hyaline or fibrosis	
Brunt, 1999 **(Brunt Criteria)**	• Steatosis with mixed inflammation, occasional ballooned hepatocytes	• Steatosis, ballooning and disarray in zone 3	• Panacinar steatosis + ballooning + disarray + portal inflammation
Kleiner, 2005 **(NAS Criteria)**	• Steatosis (0-3), lobular inflammation (0-3), ballooning (0-3) • 0-2 not NASH → ≥ 5 usually NASH		

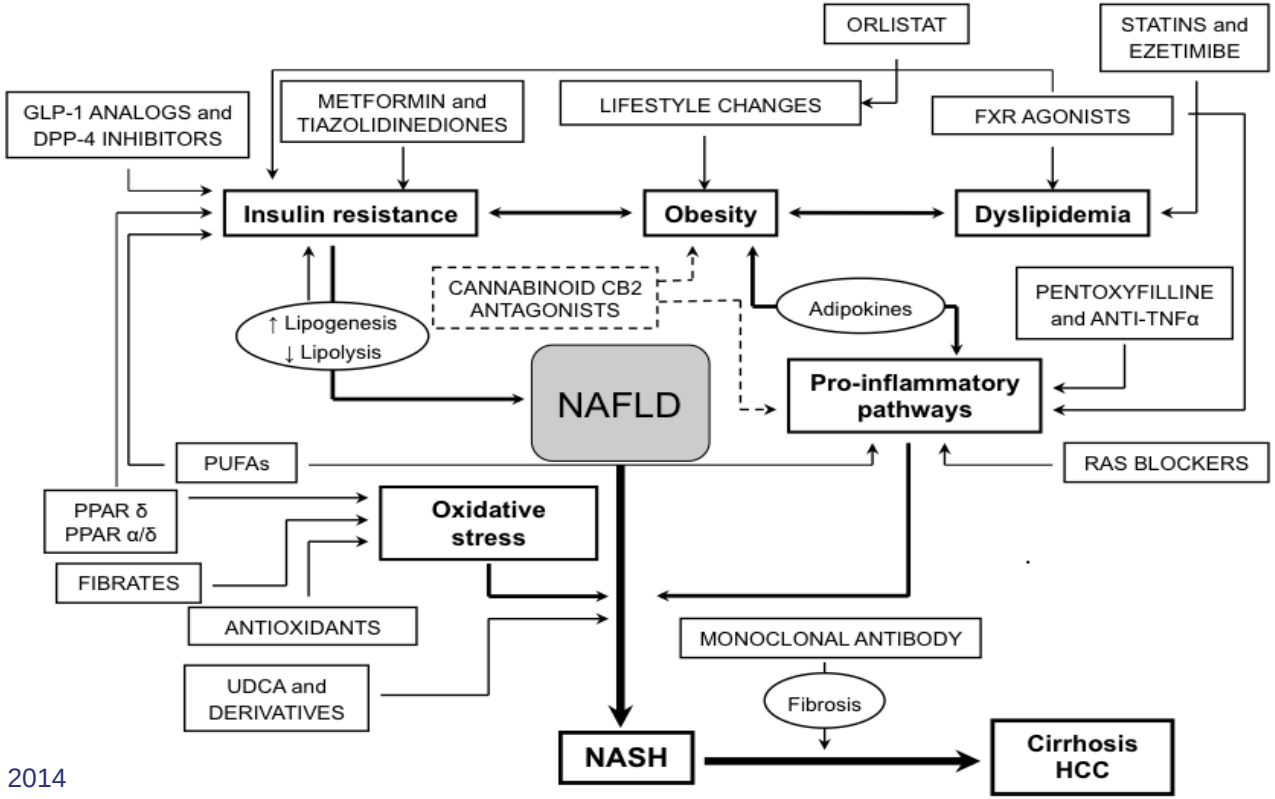
NAFLD Guideline Recommendations

Role of Biopsy

- Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis (Strength - 1, Evidence - B)
- Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy (Strength - 1, Evidence - B)

Targets for Treatment and Intervention

Targets Used for Treatment of Non-alcoholic Fatty Liver Disease



Mazzella N et al. *CLD* 2014

Treatment of NAFLD: Weight Loss

Study	N	Intervention	Duration (months)	Design	ALT*	Histology*
Hickman	31	Diet	15	Open label	+	N/A
Huang	16	Diet	12	Open label	-	+
Palmer	39	Diet	2-111	Case series	+	N/A
Andersen	41	Diet	4-23	Open label	+	+/-
Kugelmas	8	Diet/Ex	3	Open- label	+	N/A
Ueno	15	Diet/Ex	3	Open label	+	+
Zhu	34	Diet/Ex	12	Open label	+	N/A
Harrison	10	Orlistat		Open label	+	+
Sabuncu	13/12	Sibutramine/Orlistat	6	Open label	+	N/A
Luyckx	69	Surgery	27	Case series	+	+/-
Silverman	91	Surgery	2-61	Case series	+	+
Dixon	36	Surgery	26	Case series	+	+
Mummadi	766	Surgery	12	Meta-analysis	+	+

***Improvement denoted by +; No change denoted by -**

Bariatric Surgery and NAFLD

Study First Author	Year of publication	Sample size	Surgery type	Mean follow-up time	Change in Steatosis	Change in Inflammation	Change in Fibrosis	Comments
Ranlov	1990	15	RYGB or gastroplasty	12 months	↓	NR	NR	Improved liver enzymes
Silverman	1995	91	RYGB	18.4 months	↓	↓ / 0	↓	Improved lobular but no change in portal fibrosis
Luyckx	1998	69	Gastroplasty or LAGB	Not declared	↓	↓	0	NA
Dixon	2004	36	LAGB	25.6 ± 10 months	↓	↓	↓	Significant improvement in all liver panel enzymes.
Kral	2004	104	Biliopancreatic diversion (BPD)	74 ± 27 months	↓	NR	↑	Increase in fibrosis overall was small)
Clark	2005	16	RYGB	10 ± 4 months	↓	↓	↓	Improvement in lobular and portal fibrosis, ALT and AST
Keshishian	2005	78	BPD-duodenal switch (BPD-DS)	36 months	↓	↓	NR	NASH grade improved. No significant reduction in LFTs.
Mattar	2005	70	RYGB, LAGB or SG	15 ± 9 months	↓	↓	↓	
Mottin	2005	90	RYGB	12 months	↓	NR	NR	
Stratopoulos[8]	2005	216	VBG	18 ± 9.6 months	↓	↓	↓	Improvement is ALT and AST
Meinhardt	2006	30	End-to-side jejuni-ileal bypass	70 ± 42.8 months	0	0	0	No change in histology scores. ALT and AST levels tended higher.
Barker	2006	19	RYGB	21.4 months	↓	↓	↓	Improvement in portal and lobular fibrosis. Not enzymes.

Dixon J *Clinics in Liver Disease* 2014

Bariatric Surgery and NAFLD

Study First Author	Year of publication	Sample size	Surgery type	Mean follow-up time	Change in Steatosis	Change in Inflammation	Change in Fibrosis	Comments
Csendes	2006	16	RYGB	22 months	NR	NR	NR	"normalisation of histology" reported
de Almeida	2006	16	RYGB	23.5 ± 8.4 months	NR	↓	NR	Reductions in hepatocellular ballooning and lobular inflamm
Dixon	2006	60	LAGB	29.5 ± 16 months	↓	↓	↓	Improvements in inflammation and fibrosis with lowering in GGT
Klein	2006	7	RYGB	12 months	↓	NR	NR	
Furuya	2007	18	RYGB	24 months	↓	NR	↓	GGT the only enzyme to fall significantly
Liu	2007	39	RYGB	18 months	↓	NR	↓	No improvement in portal fibrosis. ALT improved
Mathurin	2006; 2009	185	BPD, LAGB, RYGB	12 & 60 months	↓	0	↑	No change 1 and 5 year fu Reduced ALT and GGT
Bell	2010	20	RYGB, LAGB, SG	15 months	↓	↓	↓	
Weiner	2010	116	LAGB, RYGB, BPD-DS	18 months	↓	↓	↓	
Tai	2011	21	RYGB	12 months	↓	↓	↓	Reduced ALT and GGT
Moretto	2012	78	RYGB	Not stated	NR	NR	↓	No overall improvement in portal fibrosis.
Vargas	2012	26	Banded - RYGB	16 months	↓	↓	↓	

Dixon J *Clinics in Liver Disease* 2014

NAFLD Guideline Recommendations

- Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity (Strength - 1, Evidence - A)
- Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation (Strength - 1, Evidence - B)
- Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown (Strength - 1, Evidence - B)

Metabolic Treatment Target: Insulin Resistance

Study	N	Drug	Duration (months)	Design	ALT	Histology
Caldwell	10	Troglitazone	3-6	Open label	+	+
Acosta	8	Pioglitazone	2-12	Open label	+	N/A
Shadid	5	Pioglitazone	4.5	Open label	+	N/A
Sanyal	21	Pioglitazone + Vit E	6	RCT	+	+
Promrat	18	Pioglitazone	12	Open label	+	+
Tetri	30	Rosiglitazone	12	Open label	+	+
Belfort	55	Pioglitazone ± Diet	6	RCT	+	+
Torres	49	R vs.R+M vs. R+Losartan	12	Open	Yes (No D)	Yes (No D)
Marchesini	14	Metformin	4	Open label	+	N/A
Nair	15	Metformin	12	Open label	+	N/A
Bugianesi	55	Metformin	6	RCT	+	+
Uygun	17	Metformin	6	RCT	+	-
Duseja	7	Metformin	6	Open label	+	N/A
Schwimmer	10	Metformin	6	Open label	+	N/A
Morita	5	Nateglinide	5	Open	Yes	Yes

NAFLD Guideline Recommendations

- Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. (Strength - 1, Evidence - A)
- Pioglitazone can be (?) used to treat steatohepatitis in patients with biopsy-proven NASH. (Strength - 1, Evidence - B)
  - However, the majority of patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic
  - Long term safety and efficacy of pioglitazone in patients with NASH is not established

Treatment: Vitamin E

Therapy	Author	N	Design	Duration (Months)	ALT Improve	Histo
Vitamin E	Lavine	11	Open	4-10	Yes	N/A
Vitamin E	Kawanaka	10	Open	6	Yes	N/A
Vitamin E	Sanyal	10	RCT	6	Yes	N/A
Vitamin E	Hasegawa	12	Open	12	Yes	Yes
Vitamin E	Vajro	14	RCT	5	No	N/A
Vitamin E	Bugianesi	25	RCT	6	No	N/A
Vitamin E/Ex	Kugelmas	8	Open	3	Yes	N/A
Vitamins E+C	Harrison	23	RCT	6	No	? Yes

NAFLD Guideline Recommendations

- Vitamin E (a-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore should be considered as a first-line pharmacotherapy for this patient population. (Strength - 1, Quality - B)
- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (Strength - 1, Quality - C)

Treatment: Lipid Lowering Agents

Study	Design (pts)	Meds	N	ALT	Hist
Laurin	Open label (12)	Clofibrate	16	-	-
Fernández-Miranda C	Open label (12)	Fenofibrate	16	+	+/-
Basaranoglu	RCT (1)	Gemfibrozil	46	+	N/A
Horlander	Open label (12)	Atorvastatin	7	+	+
Kiyici	Open label (6)	Atorvastatin	27	+	N/A
Hatzitolios	Open label (6)	Atorvastatin		+	N/A
Gomez-Dominguez	Open label (12)	Atorvastatin	25	+	N/A
Rallidis	Open label (7)	Pravastatin	5	+	+/-

NAFLD Guideline Recommendations

- Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH (Strength - 1, Quality - B)
- Until RCTs with histological endpoints prove their efficacy, statins should not be used to specifically treat NASH (Strength - 1, Quality - B)

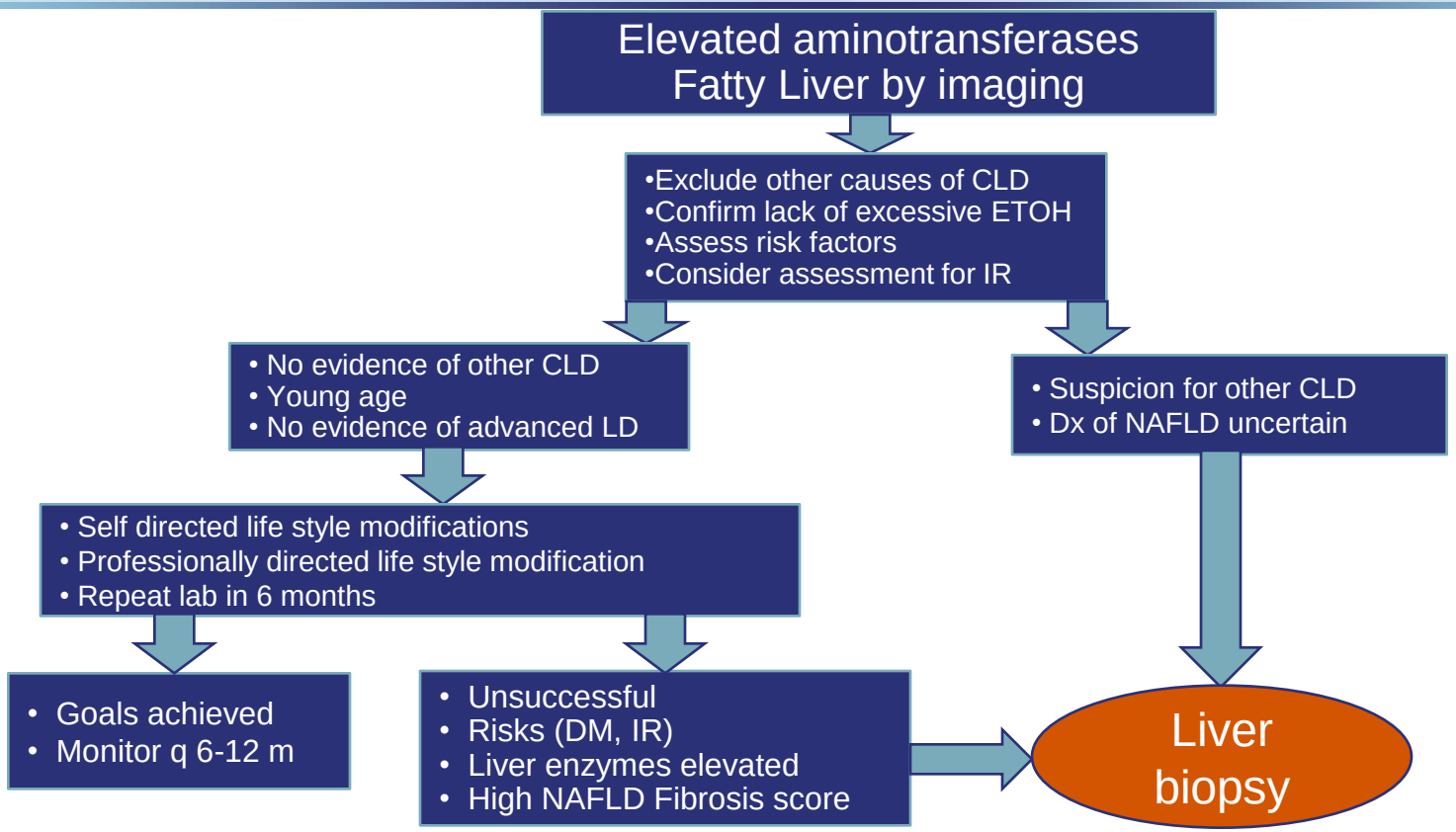
Non-alcoholic Fatty Liver Disease Other Treatment Regimens

- Antioxidants
  - Betaine
  - N-Acetyl-cysteine
  - Lecithin
  - Silymarin
  - Beta-carotene
- Anti-TNF agents (Pentoxifylline)
- Probiotics (VSL#3)
- ACE inhibitors/ARBs
- Caspase inhibitors
- Cytoprotective agents/Bile Acids
  - Ursodeoxycholic acid (UDCA)
  - Obeticholic Acid (OCA)-FLINT Study (NASH CRN)

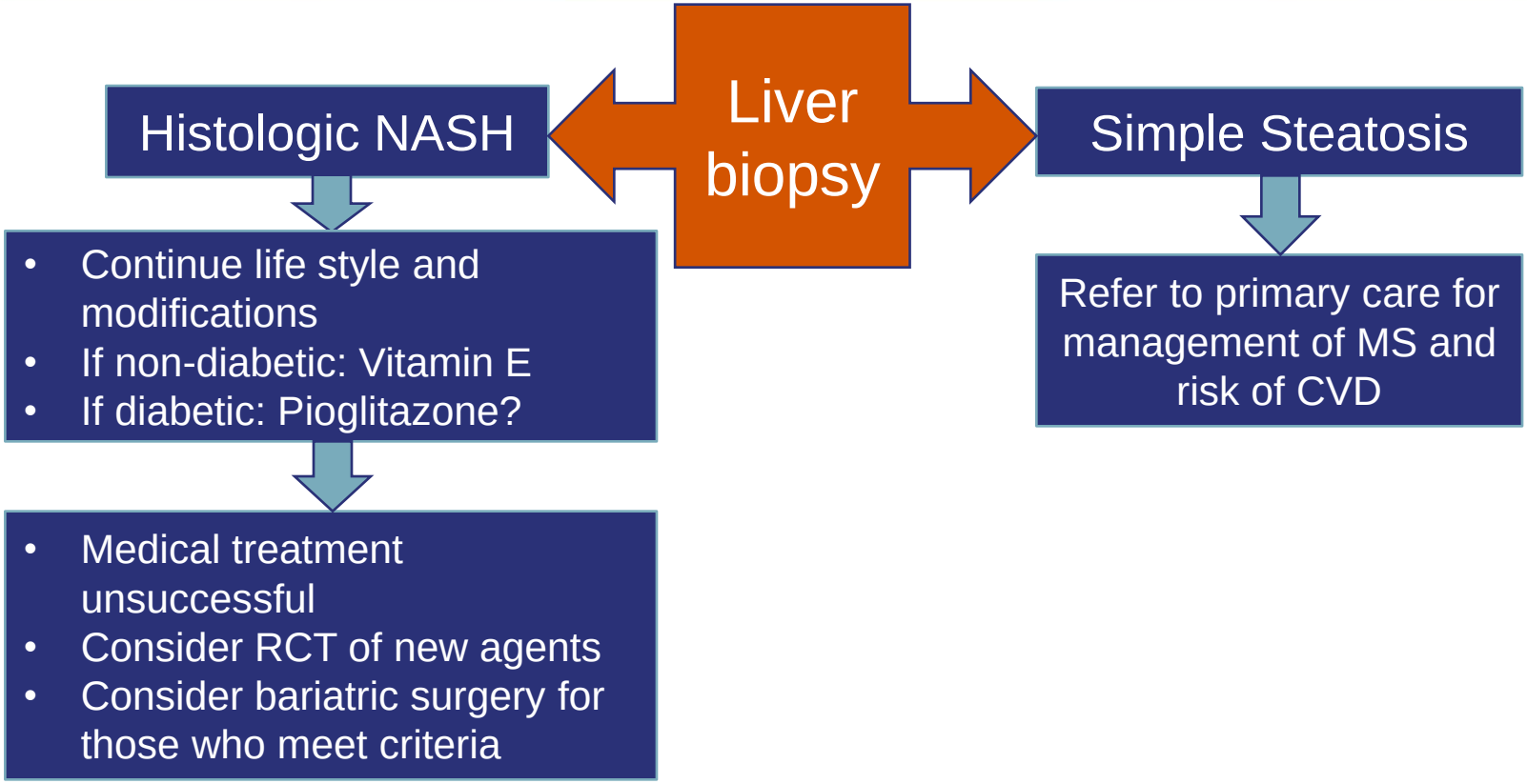
Treatment: Ursodeoxycholic Acid

Therapy	Author	N	ALT	Histology
UDCA	Laurin	24	Yes	Yes
UDCA	Holoman	24	Yes	N/A
UDCA & Diet	Ceriani	31	Yes	N/A
UDCA & Diet	Guma	24	Yes	N/A
UDCA	Kiyici	17	Yes	N/A
UDCA	Lindor	160	No	No

How Do We Manage Our NAFLD Patients in 2014?



How Do We Manage Our NAFLD Patients in 2014?



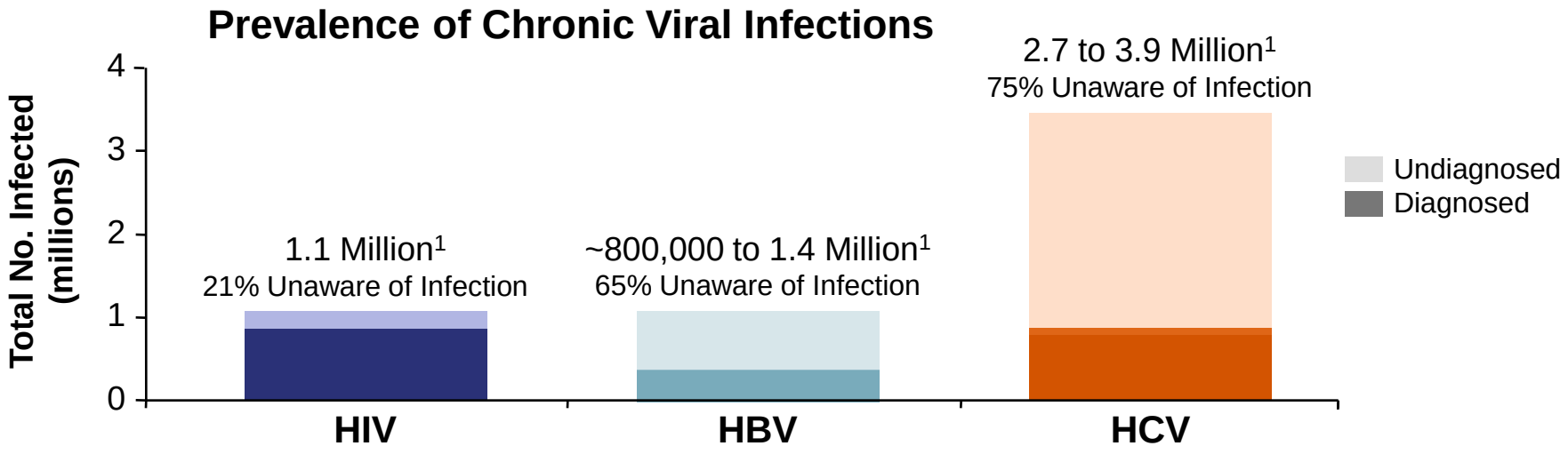
NAFLD and NASH

- NAFLD is a complex disease tied closely to obesity
- Prevalence of NAFLD parallels the epidemic of obesity
- Only NASH patients can progress
- NAFLD/NASH in the setting of DM/MS has adverse outcomes
- Lack of effective treatment from dozens of clinical trials of NAFLD suggests the heterogeneity of the NAFLD phenotype
- Personalized targeted treatment may be the best future option to treat NASH
- Some considerations for current patients with NASH:
  - Life style modifications for all
  - Vitamin E for non-DM NASH
  - ??Pio for DM with NASH but be aware of safety concerns
  - Clinical trials (OCA and others)
  - Consider bariatric surgery for morbidly obese+/-DM with NASH

HCV

Chronic Hepatitis C Infection is a Major Concern in the US

HCV is Nearly 4 Times as Prevalent as HIV and HBV

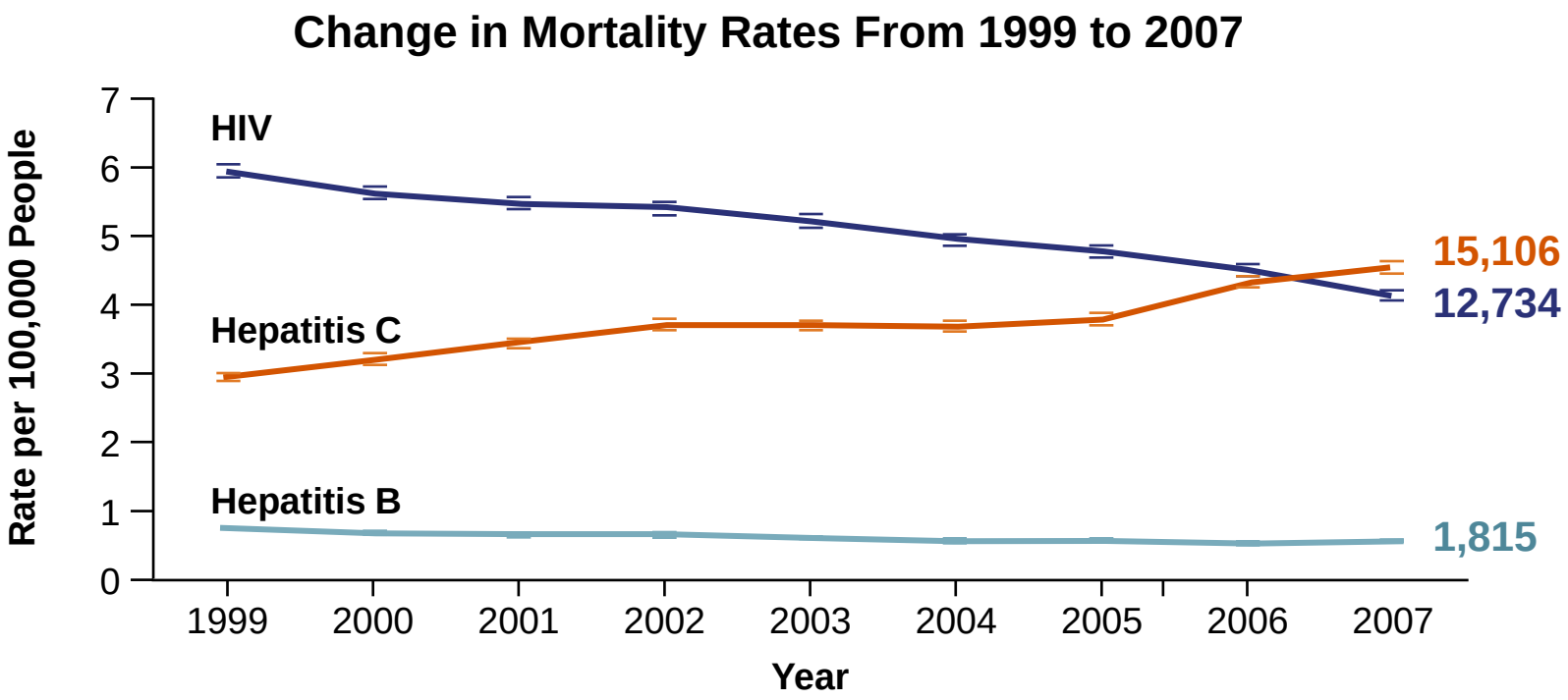


- A 2011 study estimated that as many as 5.2 million persons are living with HCV in the United States[2]

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

1. Institute of Medicine. Washington, DC: The National Academies Press; 2010.
2. Chak E, et al. *Liver Int*. 2011;31(8):1090-1101.

By 2007, Deaths From HCV Surpassed Those From HIV



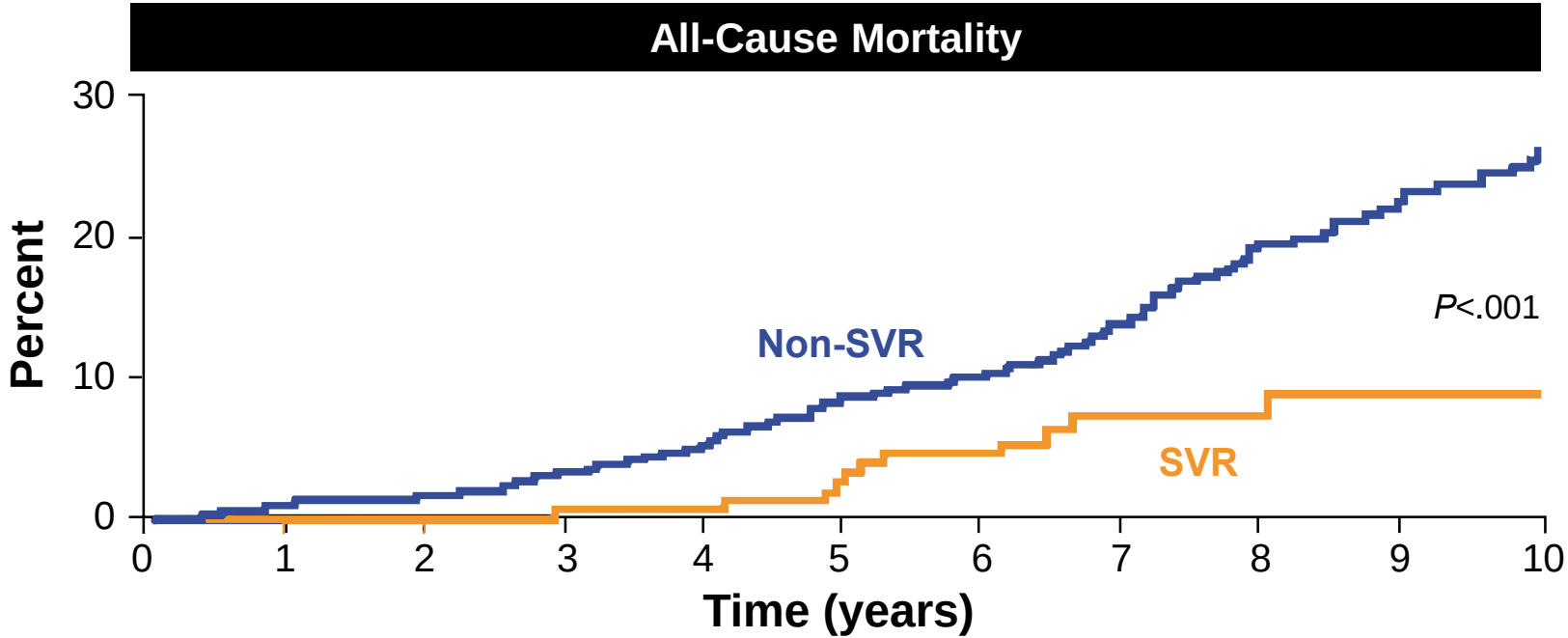
Ly KN, et al. *Ann Intern Med*. 2012;156(4):271-278.

HCV Can Now Be Cured in Most Patients

- Unlike HIV and HBV infection, HCV infection is a curable disease
- What does cure mean?
  - Sustained Viral Response
  - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection[1]
  - Long term morbidity and mortality benefits

1. Ghany MG, et al. *Hepatology*. 2009;49(4):1335-1374.

SVR Was Associated With Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

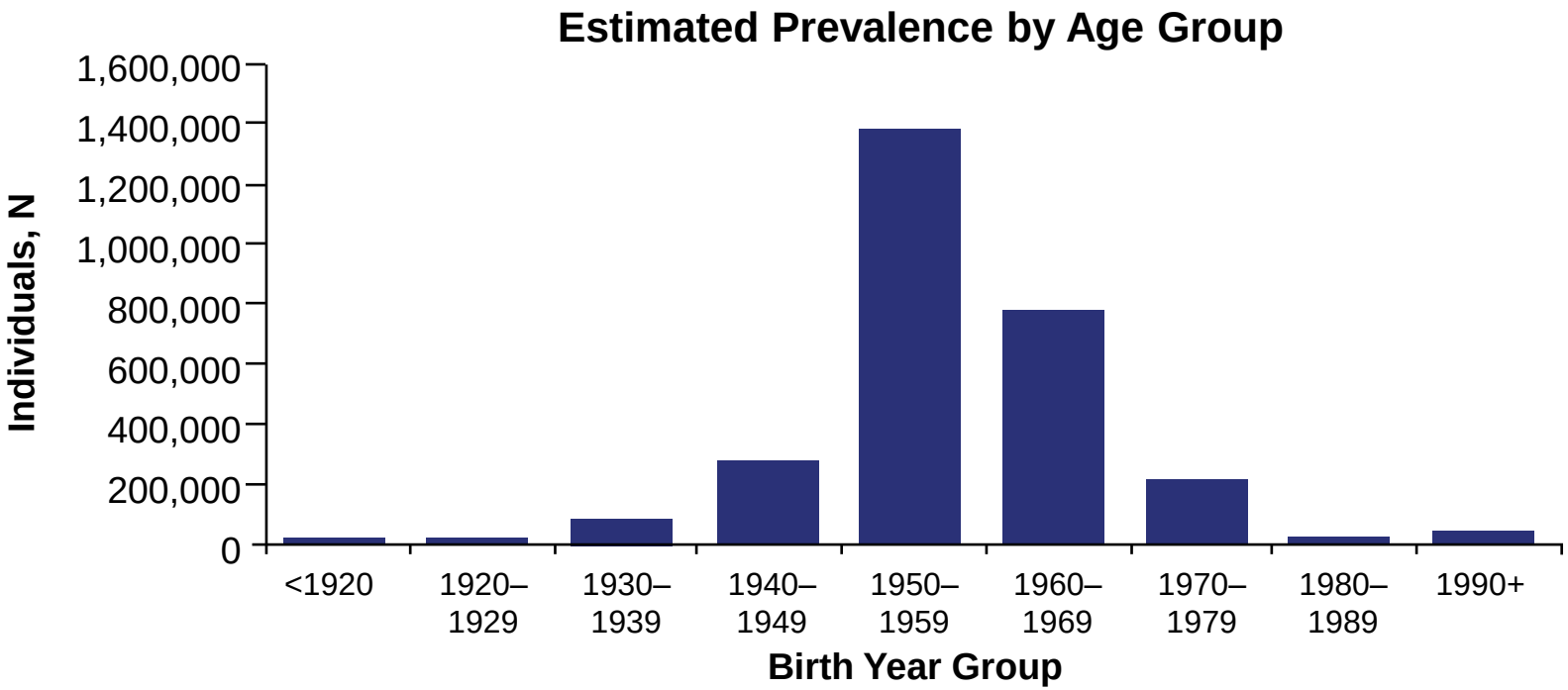


International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

Which Patients Should We Screen?

Majority of Persons Infected With HCV Are Baby Boomers (Those Born Between 1945–1965)



Centers for Disease Control and Prevention. *MMWR*. 2012;61(RR-4):1-32.

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Hepatitis C Virus Testing of Persons Born During 1945 to 1965: Recommendations From the Centers for Disease Control and Prevention

Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW.

Ann Intern Med. December 4, 2012

Who Should Be Screened for HCV ?

CDC Recommendations

- Everyone born from 1945 through 1965 (one-time)
- Persons who ever injected illegal drugs
- Persons who received clotting factor concentrates produced before 1987
- Chronic (long-term) hemodialysis
- Persons with persistently abnormal ALT levels
- Recipients of transfusions or organ transplants prior to 1992
- Persons with recognized occupational exposures
- Children born to HCV-positive women
- HIV positive persons

USPSTF Grade B Recs*

- Everyone born from 1945 through 1965 (one-time)
- Past or present injection drug use
- Sex with an IDU; other high-risk sex
- Blood transfusion prior to 1992
- Persons with hemophilia
- Long-term hemodialysis
- Born to an HCV-infected mother
- Incarceration
- Intranasal drug use
- Receiving an unregulated tattoo
- Occupational percutaneous exposure
- Surgery before implementation of universal precautions

*Only pertains to persons with normal liver enzymes; if elevated liver enzymes, need HBV and HCV testing

Smith at al. *Ann Intern Med* 2012; 157:817-822. Moyer et al. *Ann Intern Med* 2013;159(1):51-60

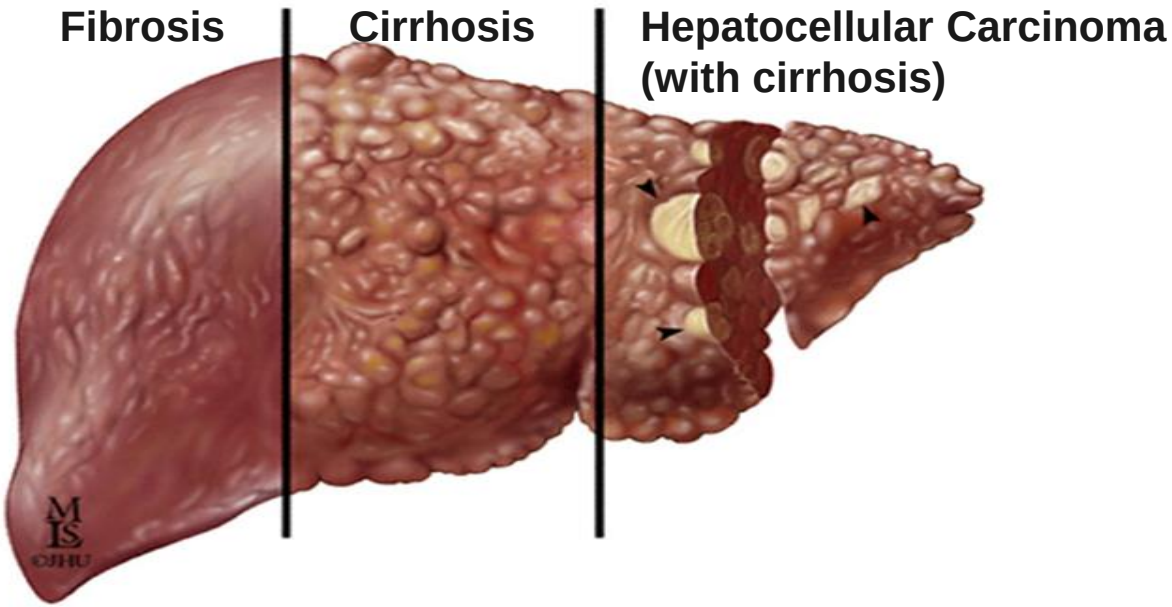
CDC and USPSTF Recommendations for HCV Screening

- Regardless of risk factors, one-time testing for HCV of adults born between 1945–1965[1,2]
  - Testing of persons of all ages *at risk* for HCV infection
- CDC also recommends for those identified with HCV infection[1]
  - Brief alcohol screening and intervention as clinically indicated
  - Referral to appropriate care and treatment services for HCV infection and related conditions

1. Centers for Disease Control and Prevention (CDC). *MMWR*. 2012;61(4):1-18
2. Moyer VA; on behalf of the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;159(1):51-60.

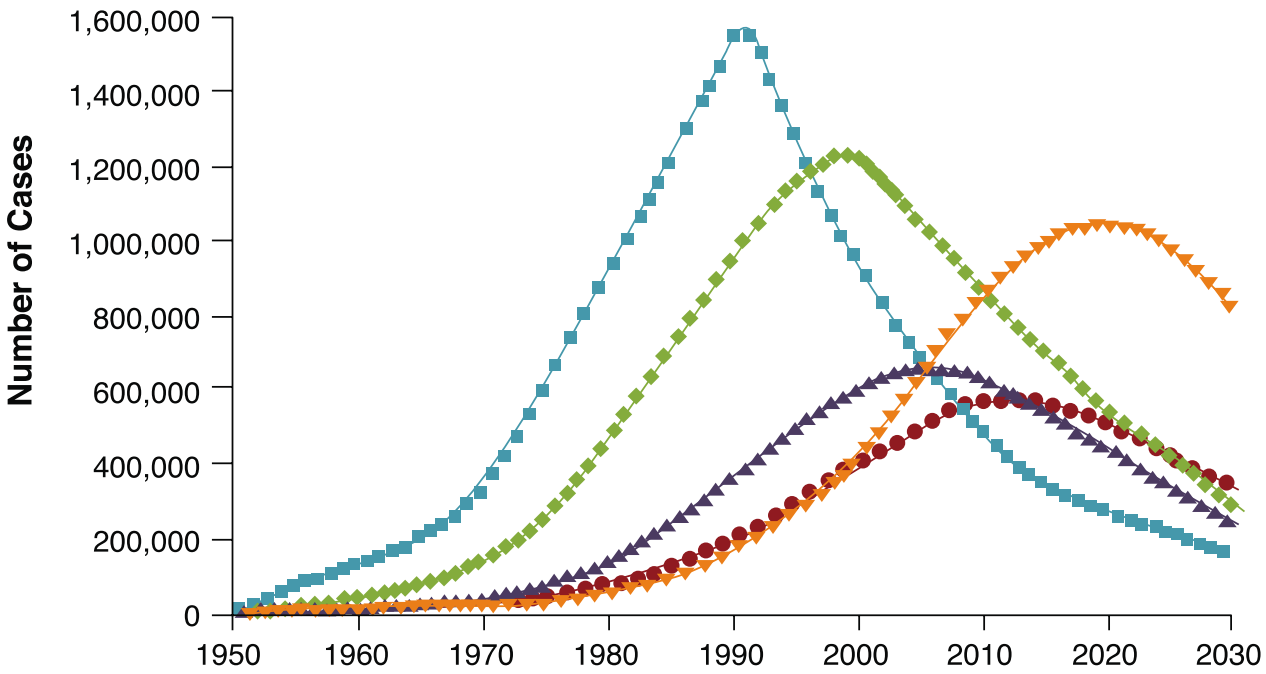
Why Screen, Diagnose and Cure?

Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer



- ~75% of patients infected with HCV will develop a chronic infection and approximately 65% of those are expected to develop chronic liver disease

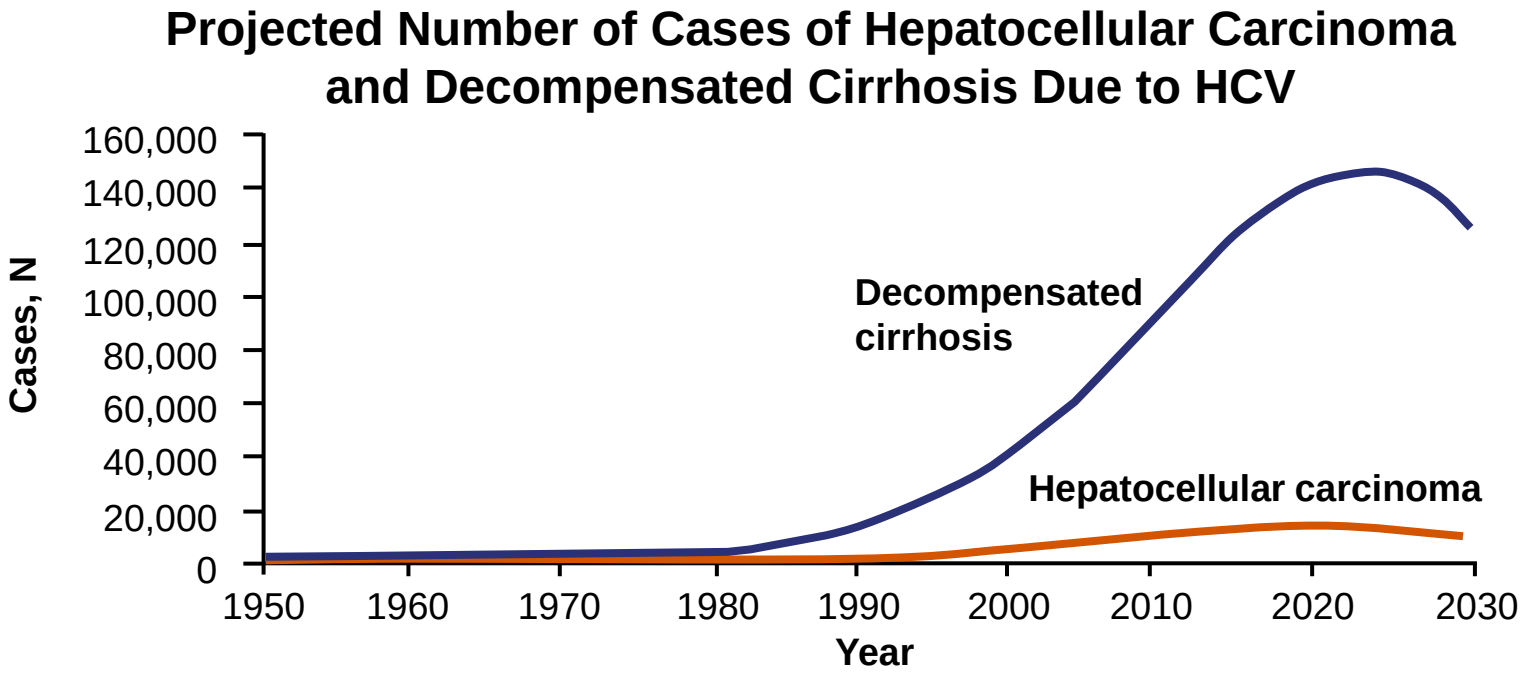
Projected Burden of Advanced Fibrosis Over the Next Decade



- 1990 → 77.6% F0/1; cirrhosis =5%
- 2010 → 41.8% F0/1; cirrhosis =25%
- 2020 → cirrhosis = **37.2%**

Davis GL, *Gastroenterology*. 2010;138:513-521.

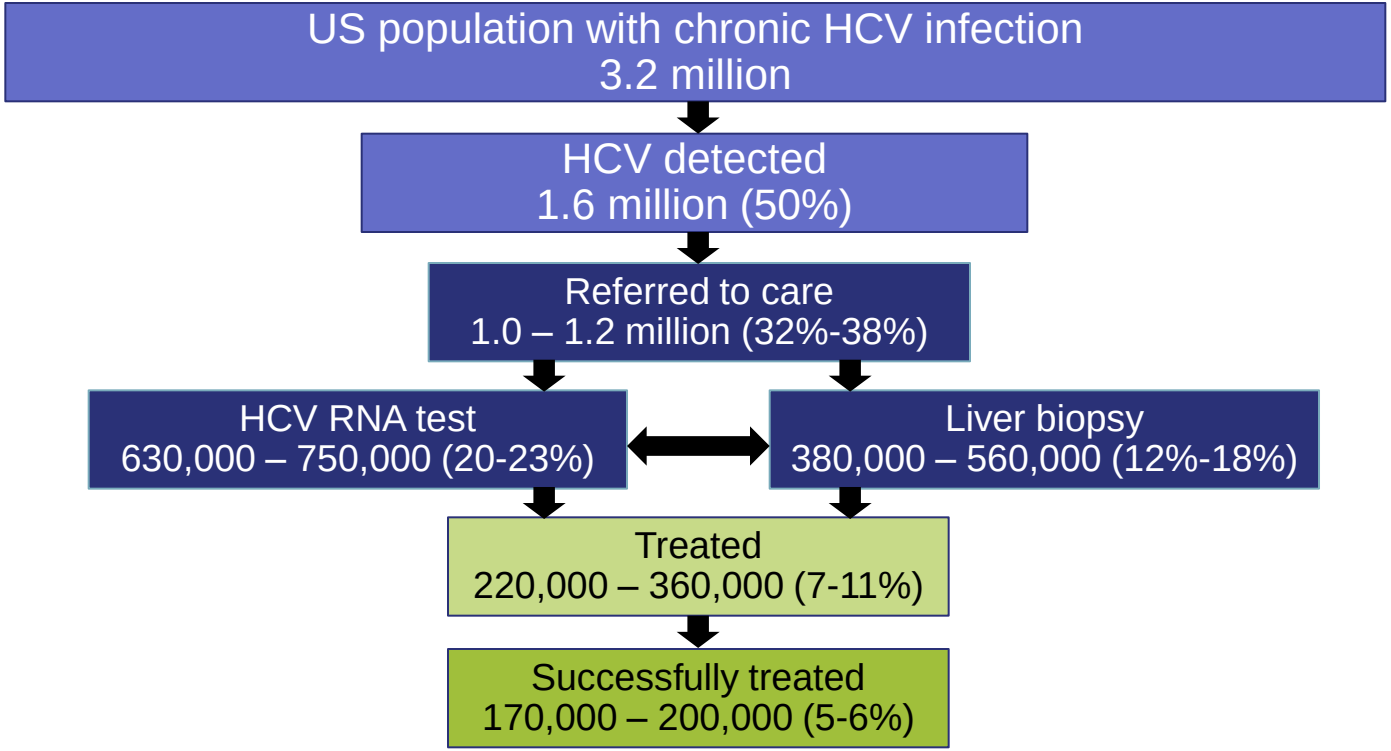
Complications Due to HCV-Related Cirrhosis Expected to Rise Over the Next 10 Years



Davis GL, *Gastroenterology*. 2010;138:513-521.

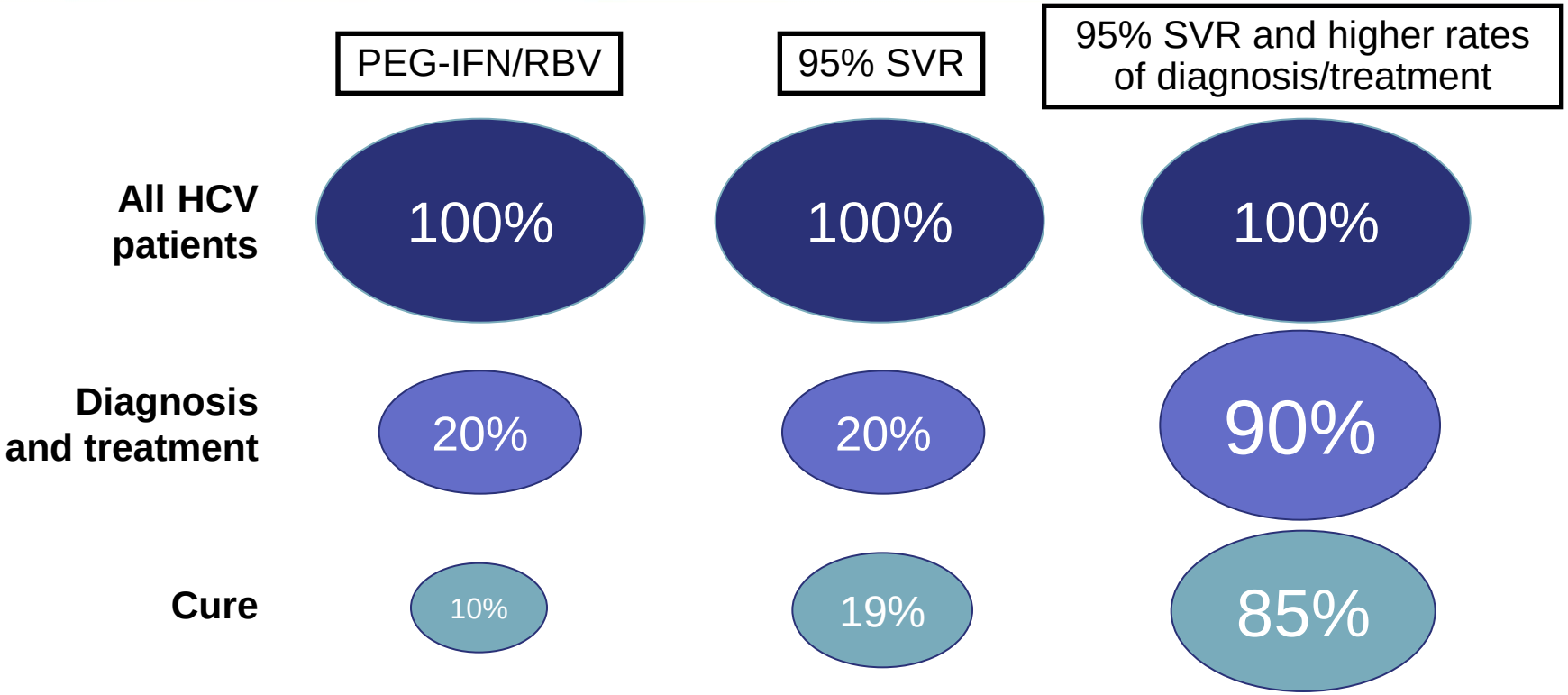
Screening and Linkage to Care

Current Status of HCV in the US: Screening and Linkage to Care Rates Remain Low



Holmberg SD et al, *New Engl J Med*. 2013; 1859-1861.

Highly Efficacious Treatments Are Not Enough



Slide courtesy of Prof. Michael Manns

Can We Predict Who Is At Higher Risk for Disease Progression?

Rate of Liver Progression is Affected by Several Patient Factors

- Male gender[1]
- Age at infection[1]
- Comorbidities such as HIV and HBV status[1]
- High levels of alcohol consumption[1]
- Immune status[1]
- Visceral obesity with steatosis[2,3]
- Diabetes[4]
- Insulin resistance[5-7]
- Synergy between risk factors[8]

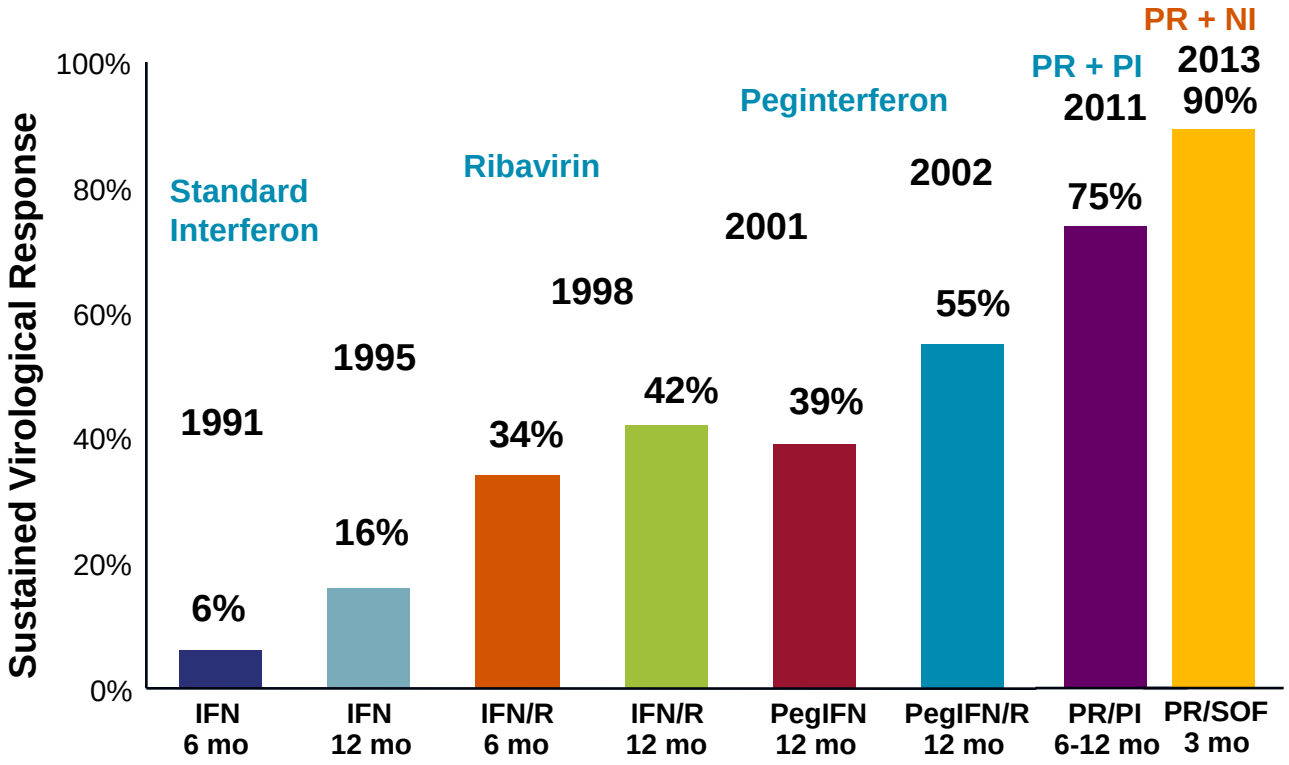
Metabolic Syndrome

Affects 37–54% of adults over 40 years old[9]

1. Chen SL, Morgan TR. *Int J Med Sci*. 2006;3(2):47-52. 2. Adinolfi LE, et al. *Hepatology*. 2001;33(6):1358-1364. 3. Adinolfi LE. *Expert Rev Gastroenterol Hepatol*. 2013;7(3):205-213. 4. El-Serag HB, et al. *Clin Gastroenterol Hepatol*. 2006;4(3):369-380. 5. Bugianesi E, et al. *J Hepatol.* 2012;56(suppl 1):S56-65. 6. Mohamed HR, et al. *Int J Health Sci (Quassim).* 2009;3(2):177-186. 7. Khattab MA, et al. *Ann Hepatol*. 2012;11(4): 487-494. 8. Loomba R, et al. *Am J Epidemiol*. 2013;177(4):333-342. 9. Ervin RB. *Natl Health Stat Report.* 2009;(13):1-7.

What Treatments Are Available and How Effective Are They?

Rapid Improvement in Treatment Options



First Direct Acting Antivirals (DAAs) for the Treatment of GT 1 Chronic Hepatitis C

- Boceprevir and telaprevir were approved in 2011
- Both compounds act by inhibiting HCV nonstructural NS3/4A protease
- Major advancement over PEG/RBV
- In 2014, use of boceprevir and telaprevir <u>not</u> recommended in AASLD/IDSA guidance document

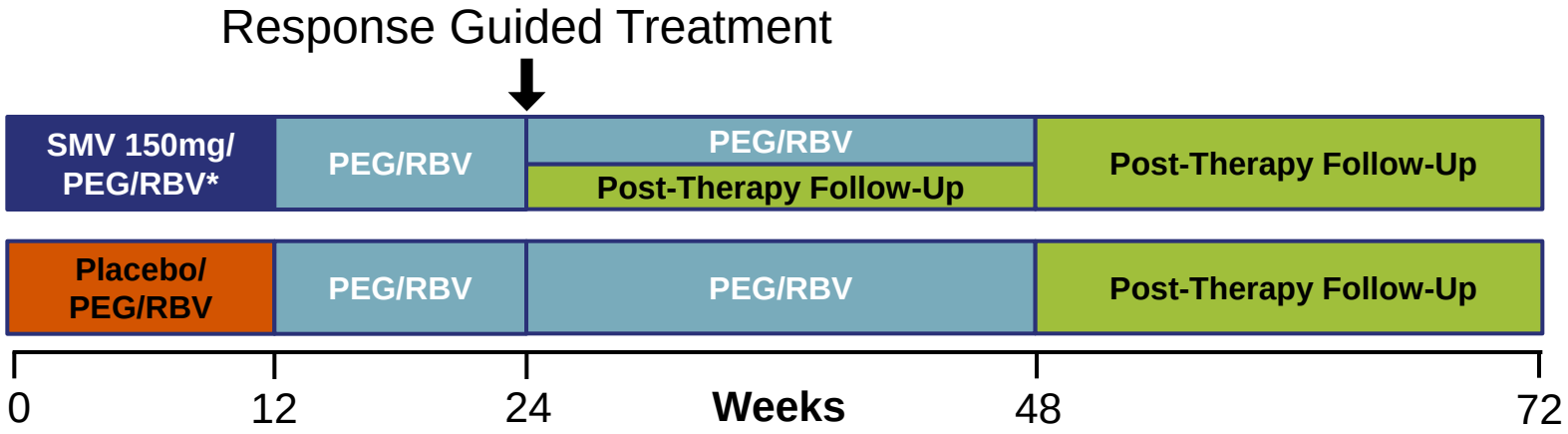
Telaprevir (INCIVEK™) Prescribing Information. Vertex Pharmaceuticals Incorporated, Cambridge, MA. October, 2013.
Boceprevir (VICTRELIS™) Prescribing Information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, September 2013.

Simeprevir (SMV) (TMC 435)

- FDA approval: November 22, 2013
- NS3/4A protease inhibitor
- One capsule taken once daily with food
- Approved for GT 1 infected subjects with compensated liver disease (including cirrhosis)
- Alternative therapy according to AASLD/IDSA guidance document

Simeprevir (OLYSIO™) Prescribing Information. Janssen Therapeutics, Titusville, NJ. November, 2013.

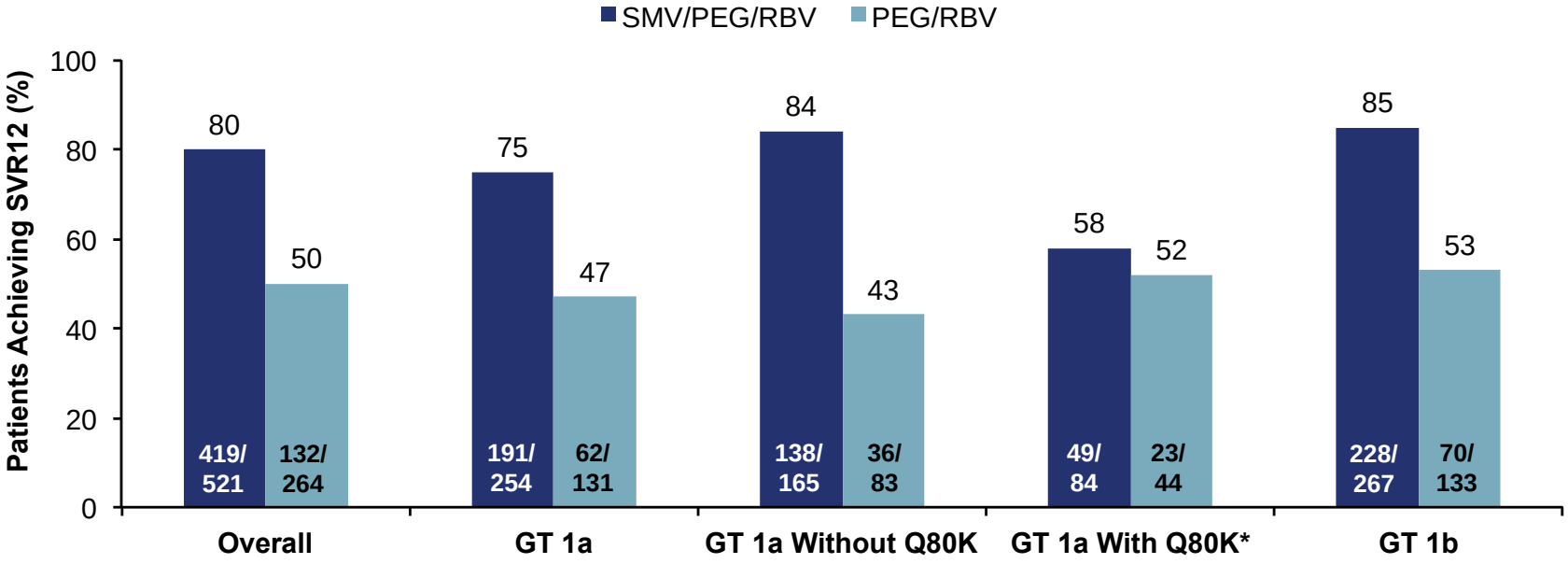
QUEST 1, QUEST 2 and PROMISE Study Designs



- Response Guided Therapy: if HCV RNA <25 International Units/mL at Week 4 and undetectable at Week 12, complete treatment at Week 24
- QUEST 1 and QUEST 2: GT 1, Treatment Naïve
- PROMISE: GT 1, Prior Relapsers

*PEG/RBV=Peginterferon/Ribavirin

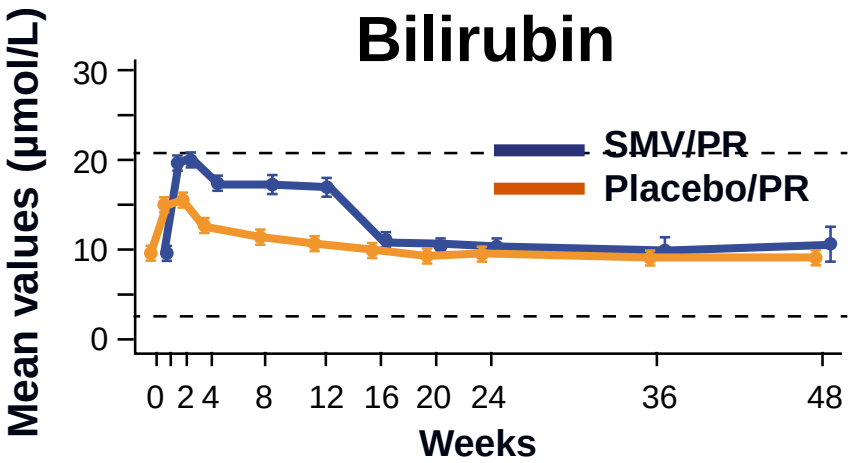
SVR12 Rates in Treatment Naive Patients (QUEST 1 and QUEST 2 Combined)

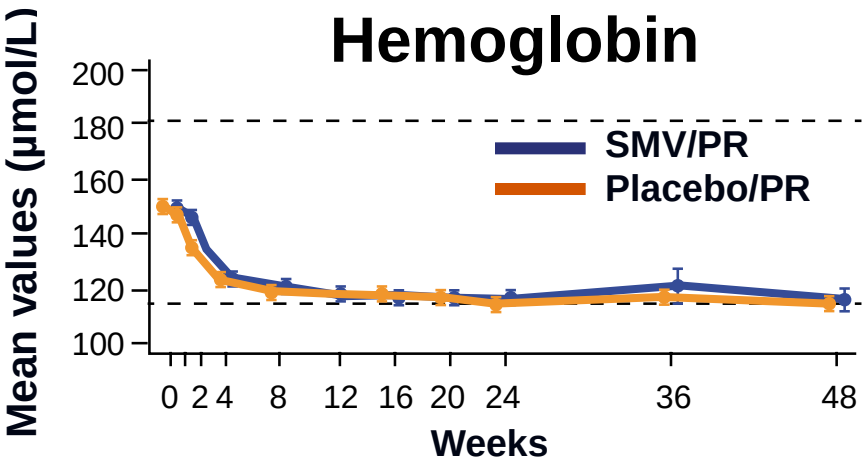


*Observed prevalence of Q80K variants at baseline in US population in the Phase 2b/3 trials: **48% of GT 1a and 0% of GT 1b patients**

Simeprevir (OLYSIO™) Prescribing Information. Janssen Therapeutics, Titusville, NJ. November, 2013.

Simeprevir is Well Tolerated





- Mild unconjugated hyperbilirubinemia → transporter
- No anemia signal beyond P/R
- Rash up to 25% (mild)

Manns M, et al. EASL 2013. Abst. 1413.

Summary of Simeprevir

Pros

- Once daily PI
- Well tolerated with less rash and no anemia
- >85% only require 6 months of treatment and most achieve SVR

Cons

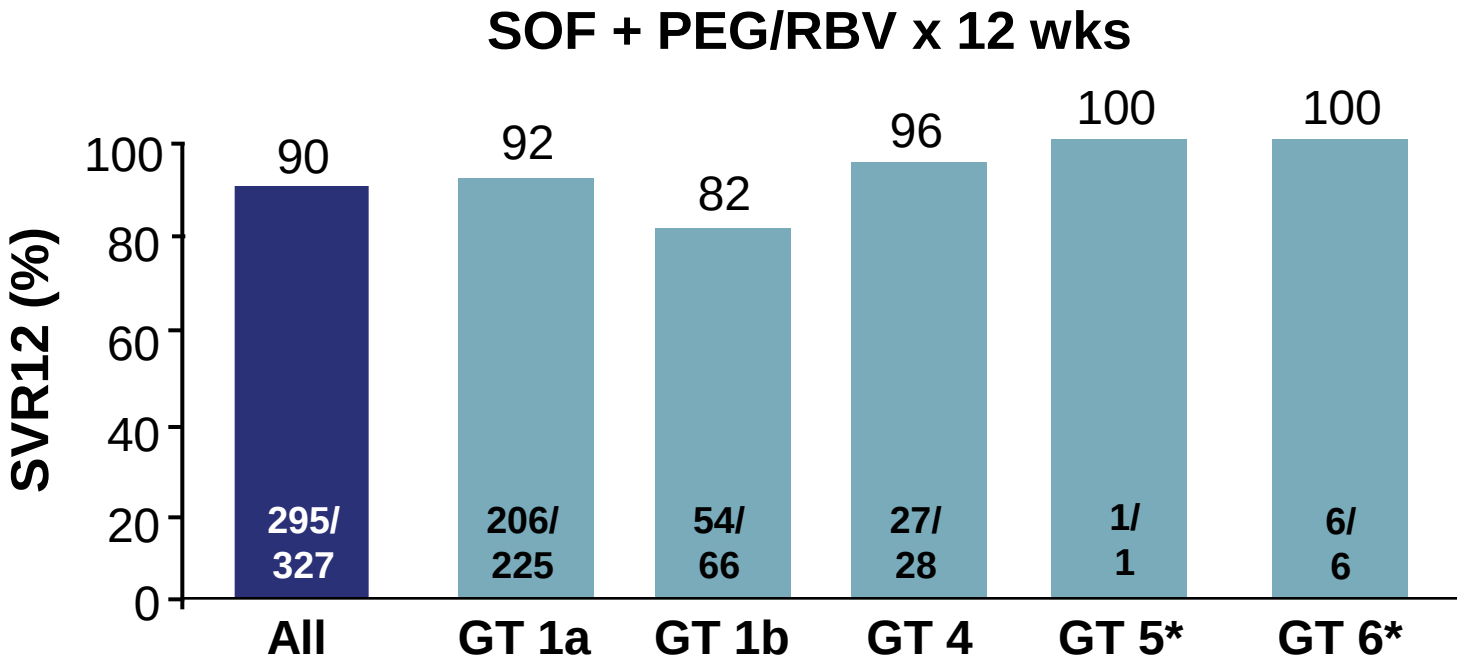
- Q80K an issue with SMV – pre-treatment testing required in all GT 1a
- DDIs still an issue – less than TVR/BOC
- Resistance profile similar to TVR/BOC when used with PEG/RBV

Sofosbuvir (SOF) (GS-7977)

- FDA approval: December 6, 2013
- Nucleotide analog NS5B polymerase inhibitor
- One oral 400 mg tablet once daily <u>with or without food</u>
- Approved for GT 1, 2, 3 and 4

Sofosbuvir (SOVALDI™) Prescribing Information. Gilead Sciences, Inc. December, 2013.

Sofosbuvir + PEG/RBV
GT 1, 4, 5 and 6 Naïve (NEUTRINO)

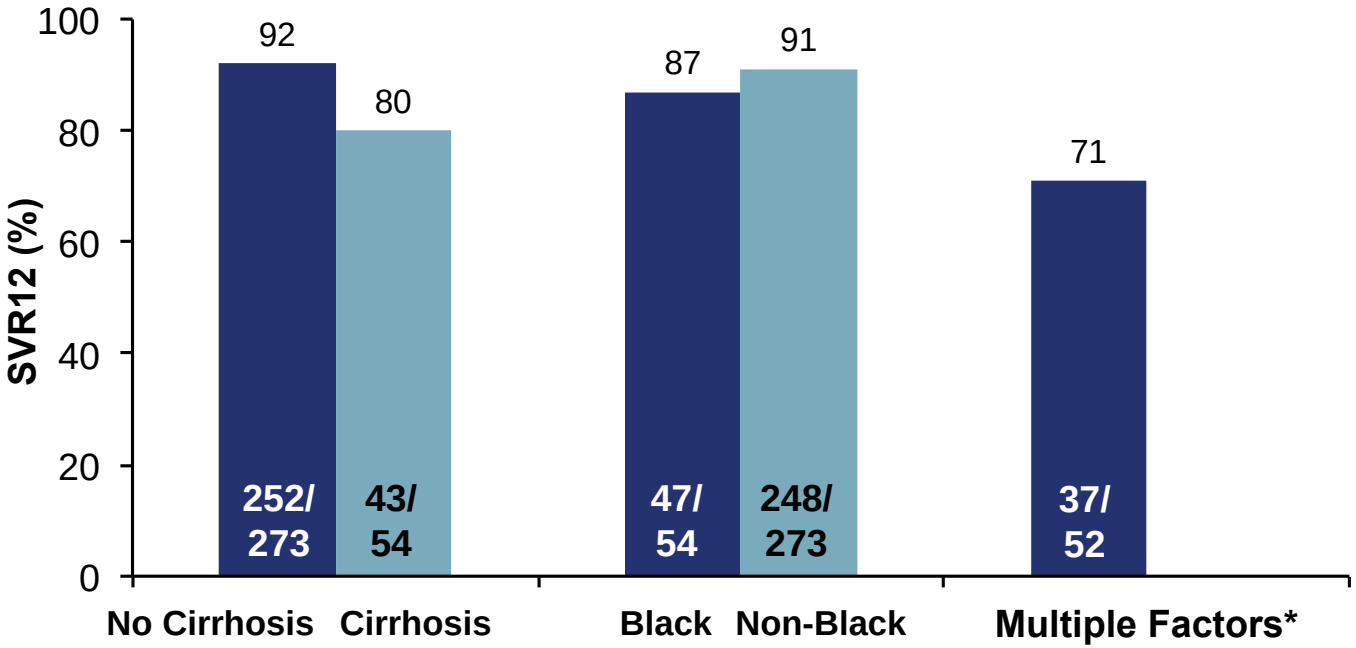


AEs similar to PEG/RBV → no control arm

*not in label

Lawitz E, et al. *NEJM* 2013

SVR Rates in Selected Subgroups (NEUTRINO)



*Patients with GT 1, METAVIR F3/F4, IL28B non-CC, HCV RNA >800,000 IU/mL (factors traditionally associated with a lower response to interferon-based treatment).

Sofosbuvir (SOVALDI™) Prescribing Information. Gilead Sciences, Inc. December, 2013.

Summary on Sofosbuvir

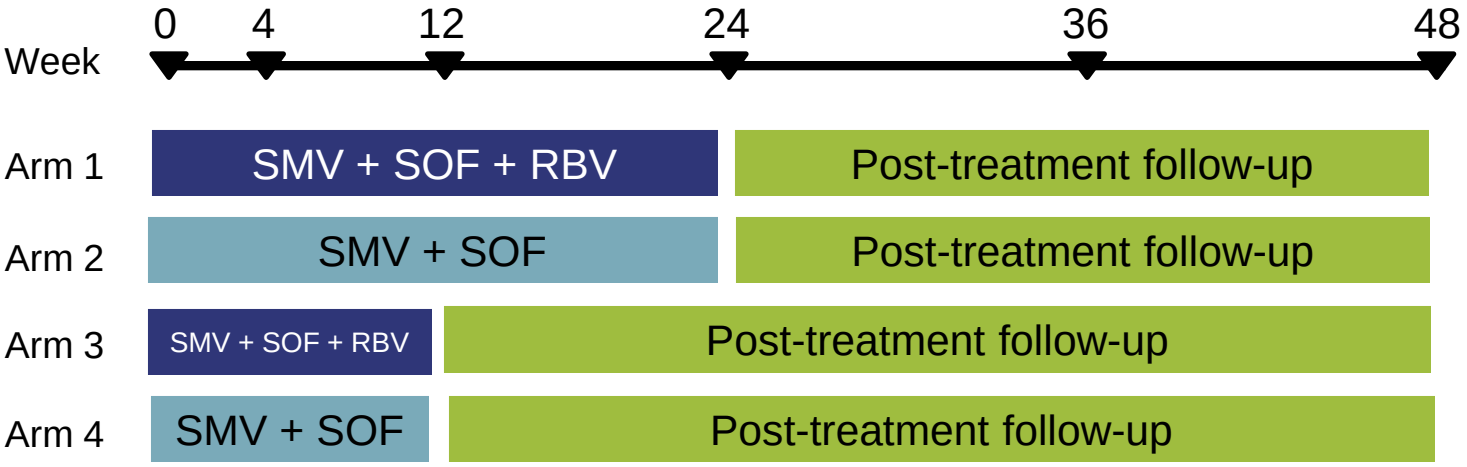
Pros

- Once daily nucleotide polymerase inhibitor
- Very well tolerated
- 12 week total treatment duration
- High SVR even in cirrhosis (80%)
- Some data in GT 4, 5 and 6
- High barrier to resistance - no breakthrough → only few relapses

Cons

- No control group
- No clinical trial data in treatment experienced – naïve only

SOF+SMV: All Oral 12 Week Treatment Option? (COSMOS)

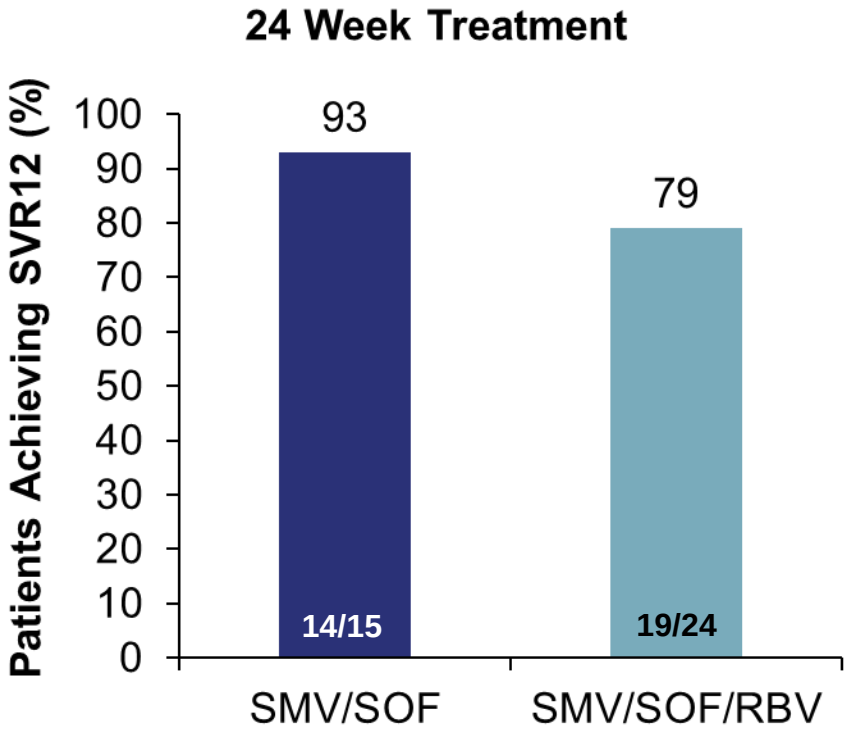


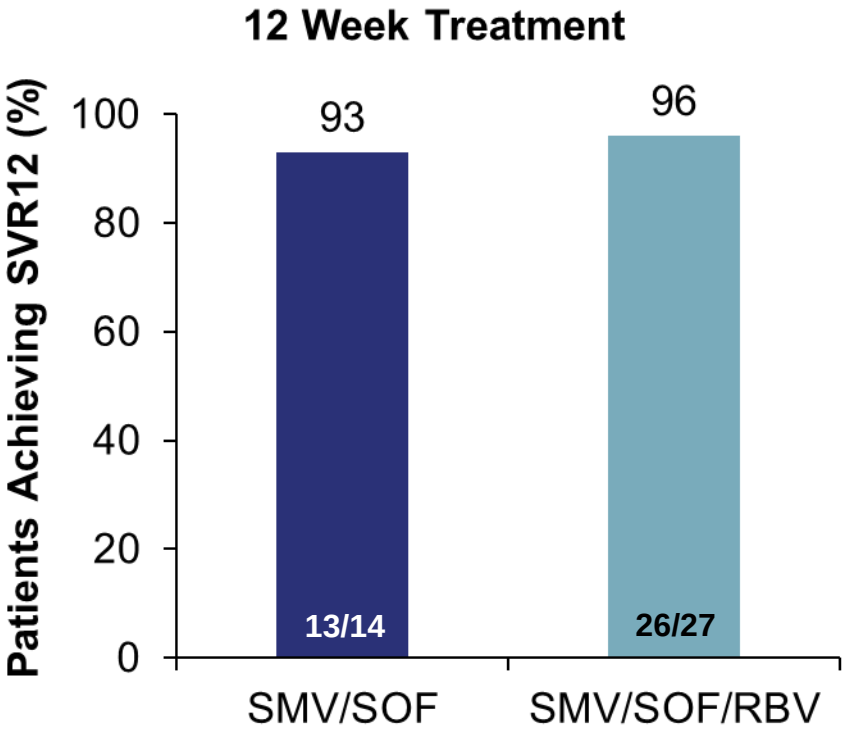
Enrollment ratio 2:1:2:1

- Cohort 1: Prior null responders (METAVIR F0-F2)
- Cohort 2: Treatment-naïve and prior null responders (METAVIR F3-F4)

Jacobson IM, et al. Abstract #LB-3, AASLD 2013

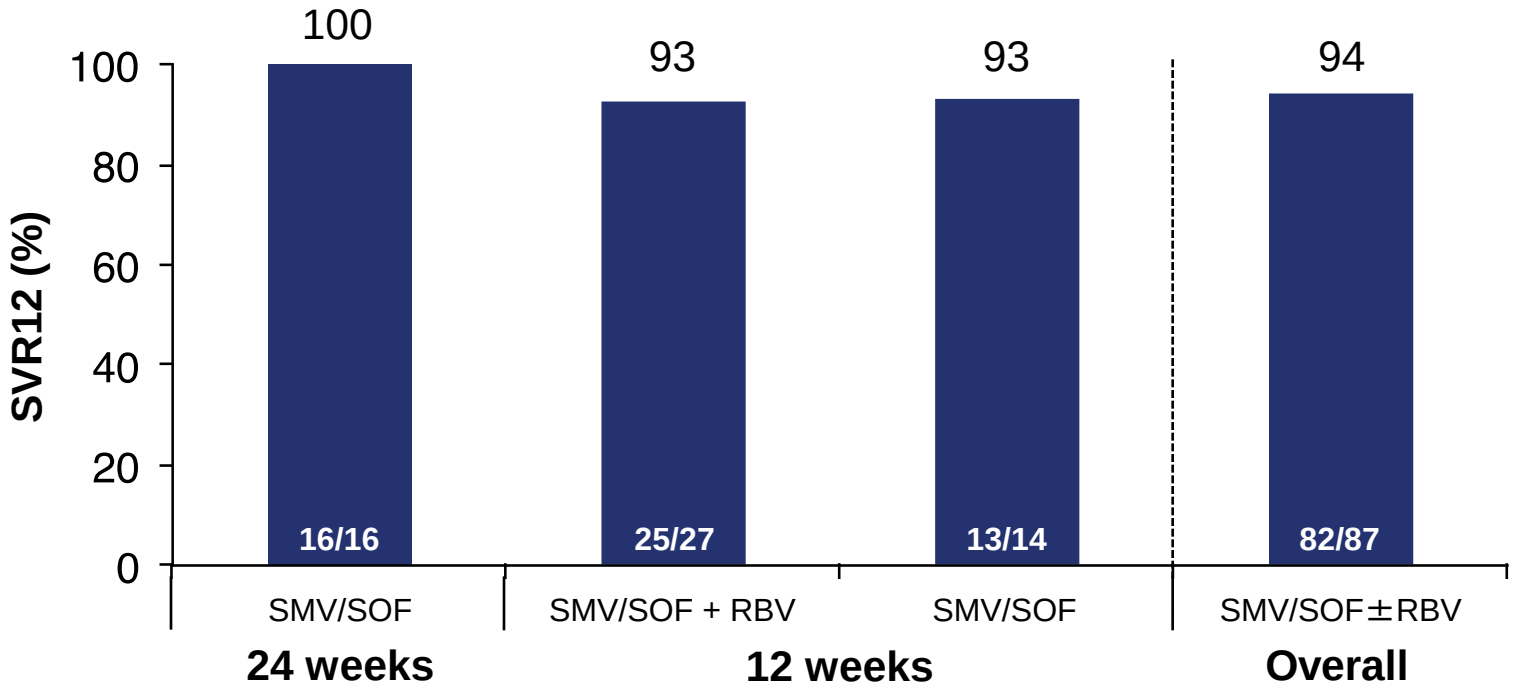
All Oral Regimen in Null Responders (F0-F2) Treated For 12 Weeks





Jacobson IM, et al. Abstract #LB-3, AASLD 2013

Treatment Naïve and Null Responders (F3-F4) With All Oral Regimen For 12 Weeks



Lawitz, E. et al. EASL 2014, Abstract #O165

COSMOS: Safety and Tolerability in Treatment Naïve and Null Responders (F3-F4)

Patients, n (%)	24 weeks		12 weeks		
	SMV/SOF + RBV (N=30)	SMV/SOF (N=16)	SMV/SOF + RBV (N=27)	SMV/SOF (N=14)	Total (N=87)
Grade 3 or 4 AEs	5 (16.7)	2 (12.5)	1 (3.7)	1 (7.1)	9 (10.3)
Any serious AE (SAE)	3 (10.0)	1 (6.3)	0	0	4 (4.6)
AE leading to discontinuation of all study drugs	0	1 (6.3)	0	0	1 (1.1)
Death during treatment	1 (3.3)*	0	0	0	1 (1.1)

*Fatal accident (not related to study medication)
AE, adverse event; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

SOF+SMV Combination Therapy

- Not in FDA prescribing information for either drug
- However, treatment guidance document recommends the regimen for IFN-intolerant patients with GT 1 infection

Sofosbuvir/Ledipasvir Fixed Dose Combo

- Sofosbuvir (SOF) is a potent nucleotide polymerase inhibitor
- Ledipasvir (LDV) is a potent NS5A inhibitor
- Co-formulated SOF/LDV was used in Phase 3 studies
- Approved by FDA October 10, 2014

Treatment Duration

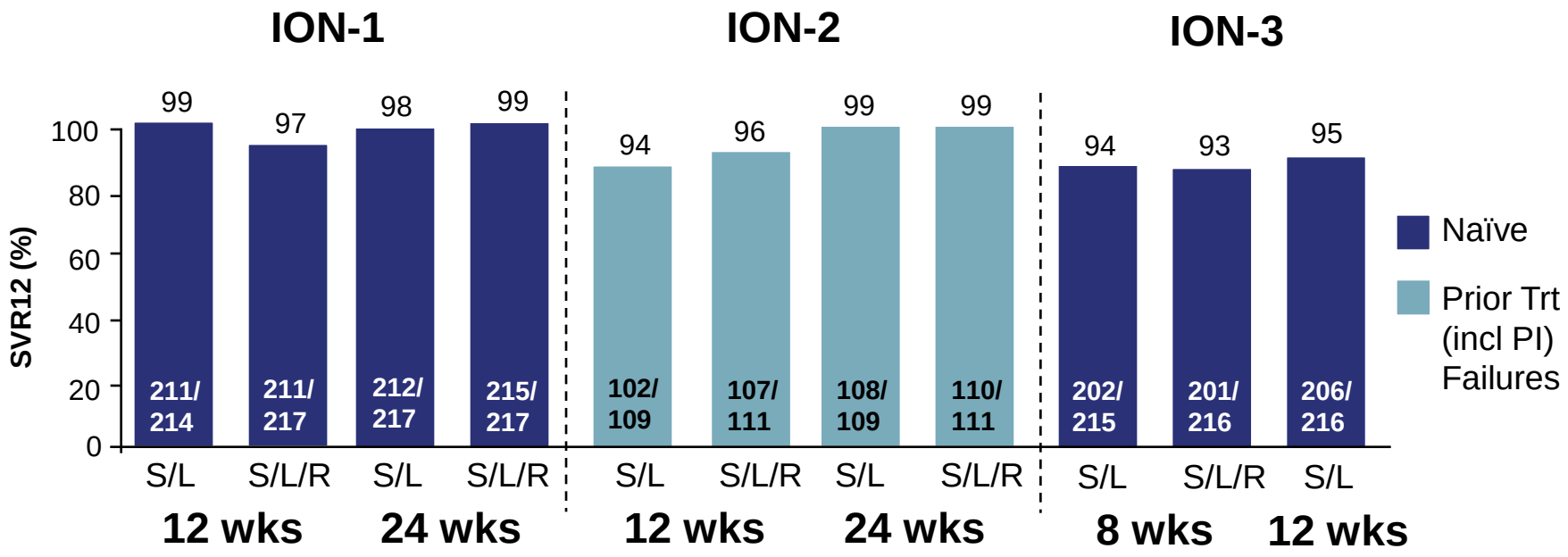
Patient Population	Recommended Treatment Duration
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced** without cirrhosis	12 weeks
Treatment-experienced** with cirrhosis	24 weeks

* Treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL can be treated with **8 weeks** of therapy

** Treatment-experienced patients who previously failed treatment with either PEG/RBV or a PI/PEG/RBV

Ledipasvir/sofosbuvir (HARVONI™) Prescribing Information. Gilead Sciences, Foster City, CA. October, 2014.

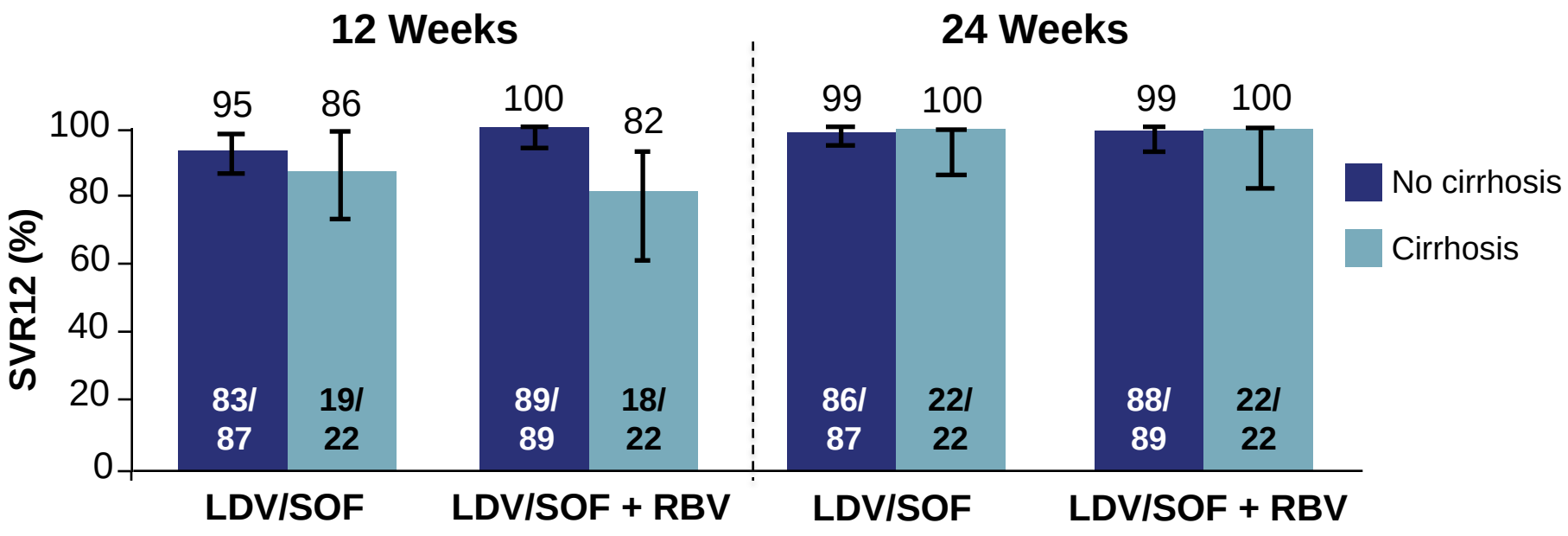
Sofosbuvir + Ledipasvir ± RBV



S/L=sofosbuvir/ledipasvir; S/L/R=sofosbuvir/ledipasvir/ribavirin

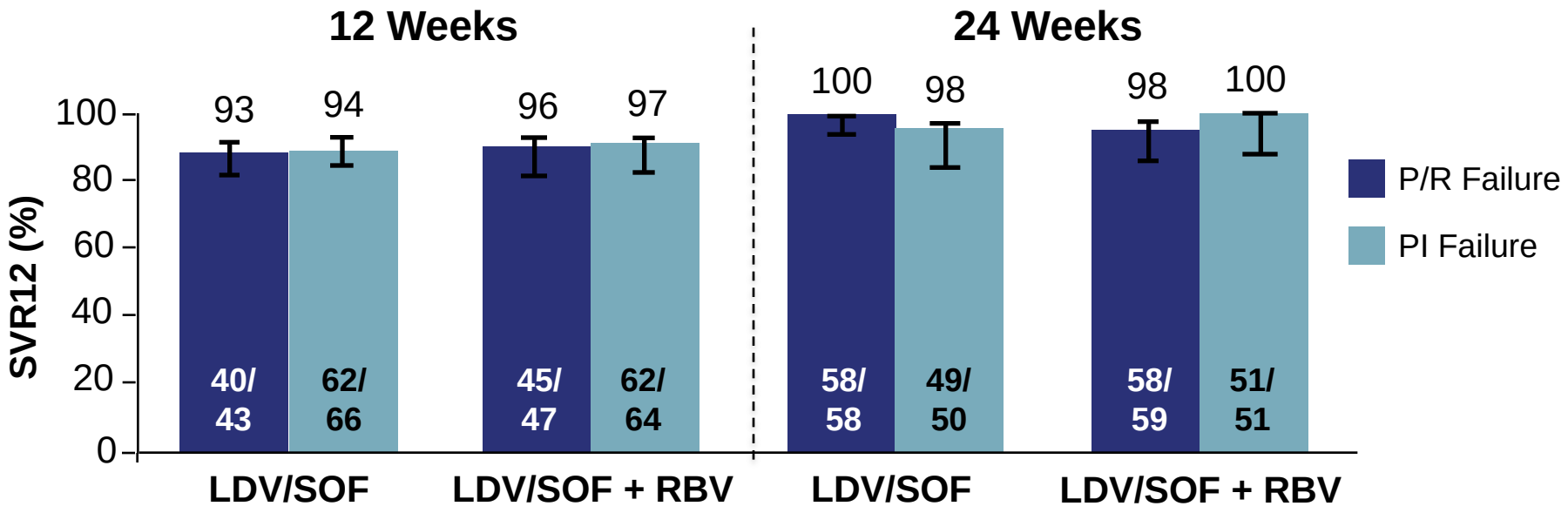
Mangia EASL 2014, Afdhal EASL 2014, Kowdley EASL 2014

SOF/LDV ± RBV in Treatment-Experienced Patients With Cirrhosis (ION-2)



Afdhal EASL Abst O109

SOF/LDV ± RBV for Prior PI Failures (ION-2)



- No cross resistance with PI and either SOF/LDV

Afdhal EASL Abst O109

SOF/LDV Summary

- Very effective single pill regimen
- RBV does not appear necessary
- No difference GT 1a vs GT 1b
- Very well tolerated
- No issue with resistance

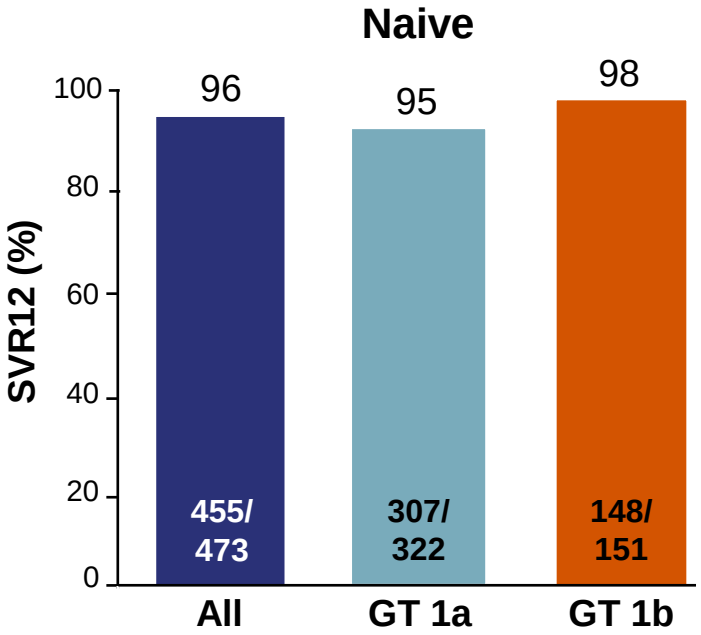
Near Term Options For GT 1 (Not Currently Approved)

3D Regimen

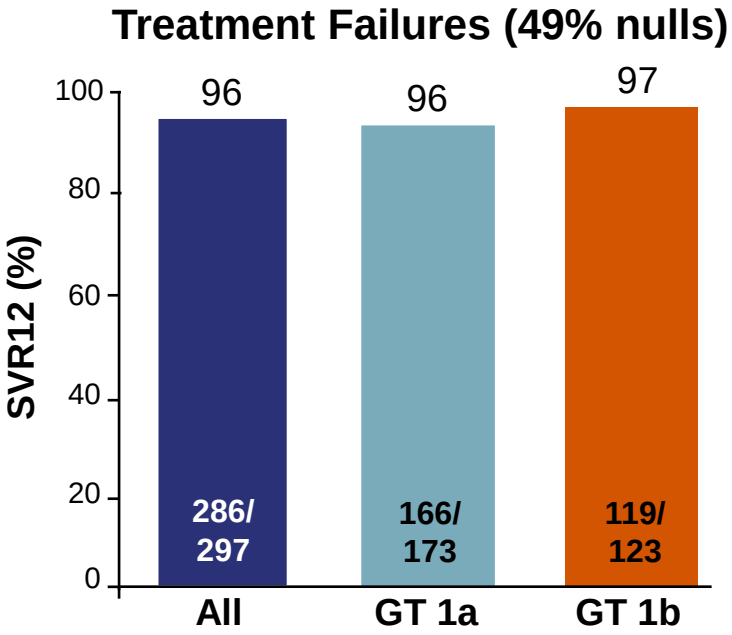
- ABT-450 is a potent NS3/4A protease inhibitor
  - Co-dosing of ABT-450 with ritonavir (ABT-450/r) increases the peak, trough, and overall drug exposures of ABT-450, and also enables once daily dosing
- Ombitasvir (formerly ABT-267) is a potent NS5A inhibitor
- Dasabuvir (formerly ABT-333) is a non-nucleoside NS5B polymerase inhibitor
- Co-formulated ABT-450/r/ombitasvir was used in Phase 3 studies
- Known as the “3D Regimen”

3D Regimen + RBV (PEG Free)(SAPPHIRE I/II)

12 week treatment duration

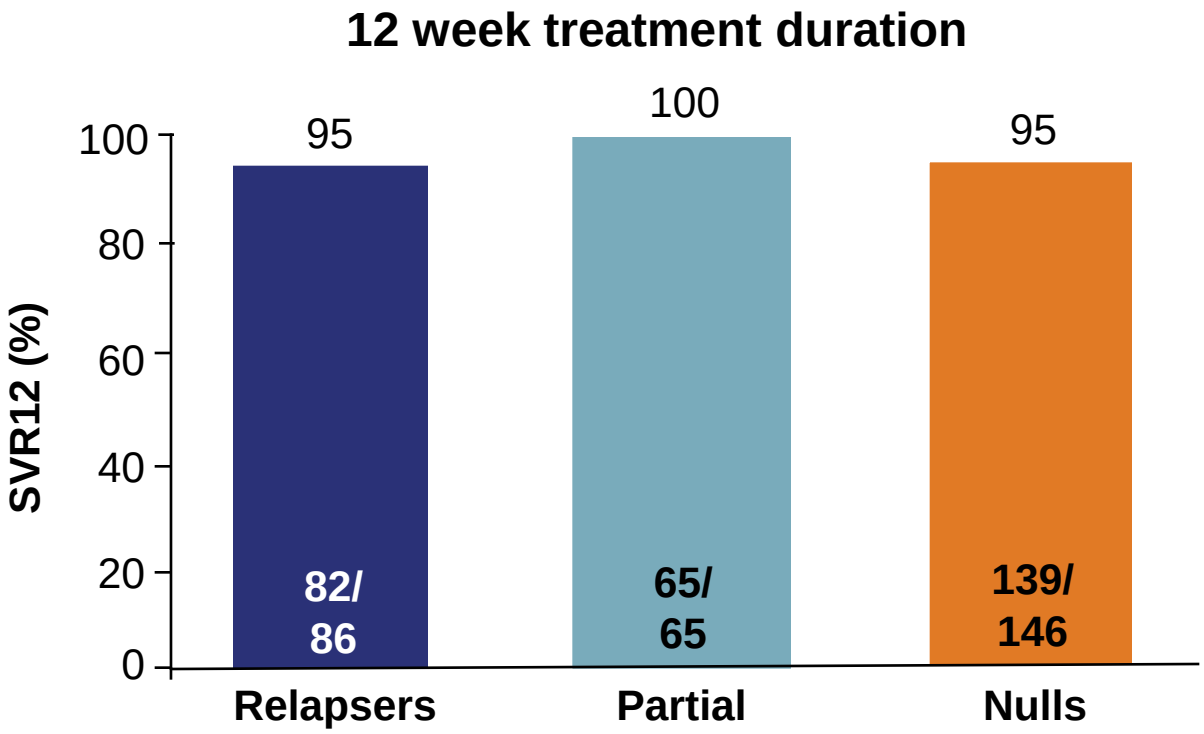


Feld J EASL 2014 Abst 060, *NEJM* 2014



Zeuzem S EASL 2014 Abst 01, *NEJM* 2014

3D Regimen + RBV for Prior Nonresponders (SAPPHIRE II)



Zeuzem S EASL 2014 Abst 01, *NEJM* 2014

3D Regimen + RBV: Safety/Tolerability

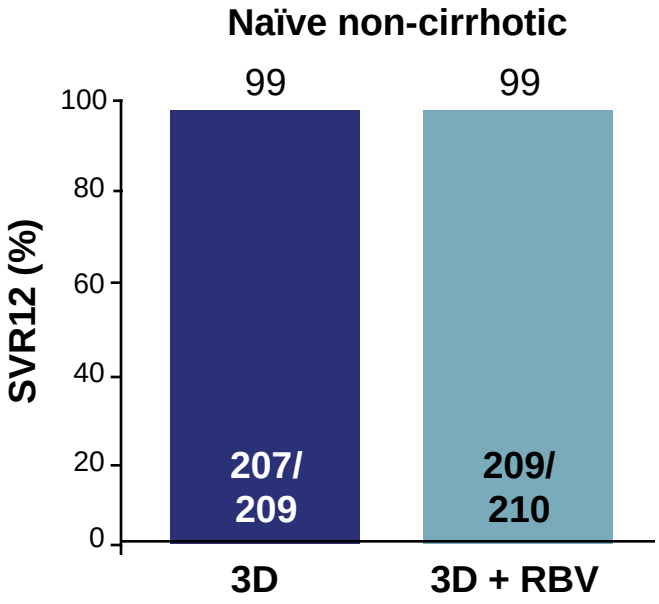
Adverse Events (AEs)	SAPPHIRE I		SAPPHIRE II	
	3D + RBV (n = 473)	Placebo (n = 158)	3D + RBV (n = 297)	Placebo (n = 97)
Any AE, n (%)	414 (87.5)	116 (73.4)	271 (91.2)	80 (82.5)
AE leading to D/C, n (%)	3 (0.6)	1 (0.6)	3 (1.0)	0
Any serious AE, n (%)	10 (2.1)	0	6 (2.0)	1 (1.0)
Grade 3/4 lab events, n/N (%)				
▪ ALT>5x ULN	4/469 (0.9)	7/158 (4.4)	5/296 (1.7)	3/96 (3.1)
▪ Creatinine	--	--	2/297 (0.7)	0
▪ **Total bilirubin**	**13/469 (2.8)**	**0**	**7/296 (2.4)**	**0**
▪ Hemoglobin 8-10 g/dL*	27 (5.8)	0	14/296 (4.7)	0

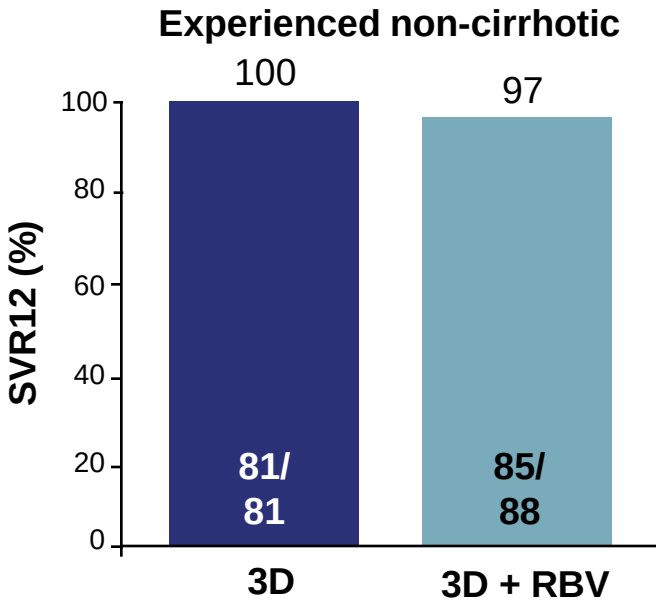
- ALT improved with continued dosing
- Bilirubin – total, related to transporter inhibition
- No one met Hy's law → not hepatotoxicity
- Anemia – RBV dose reduction 5.5-6.4%, no effect on SVR

Feld J EASL 2014 Abst 060, *NEJM* 2014; Zeuzem S EASL 2014 Abst 01, *NEJM* 2014

3D Regimen +/- RBV in GT 1b Patients (PEARL III)

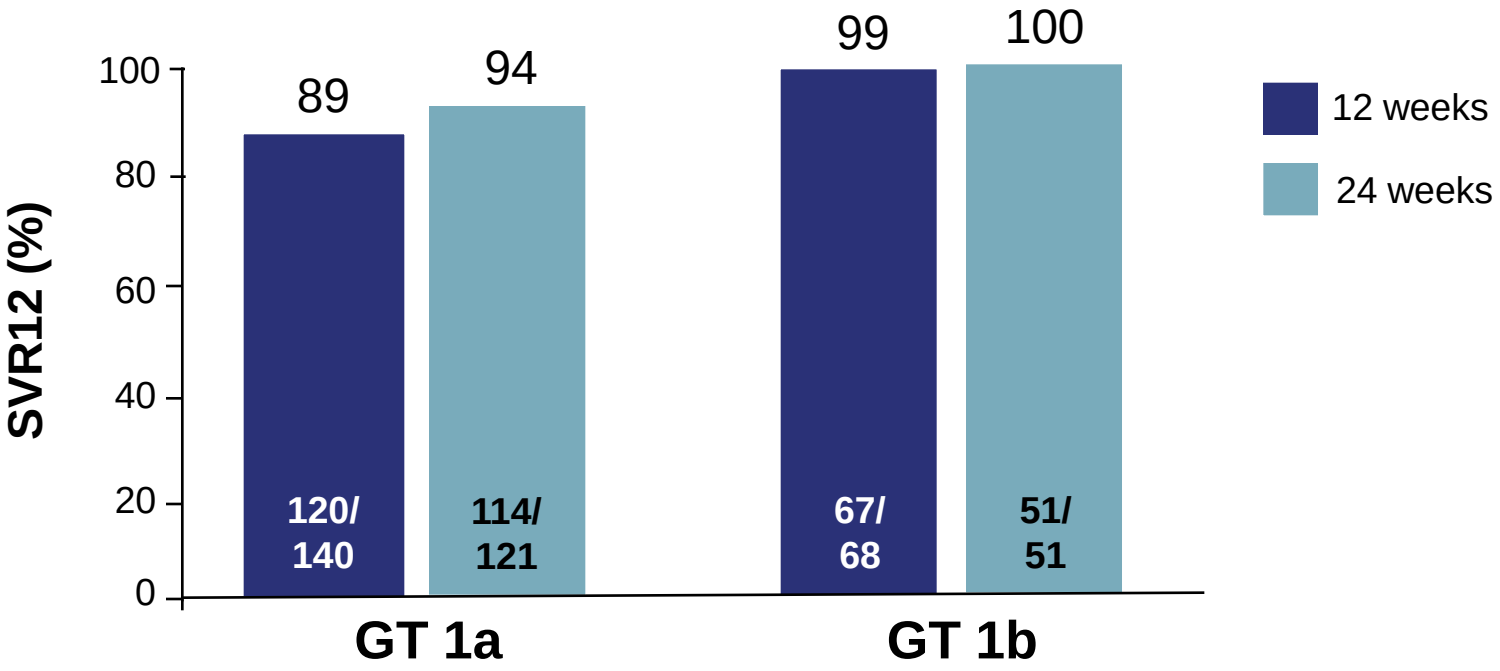
12 week treatment duration





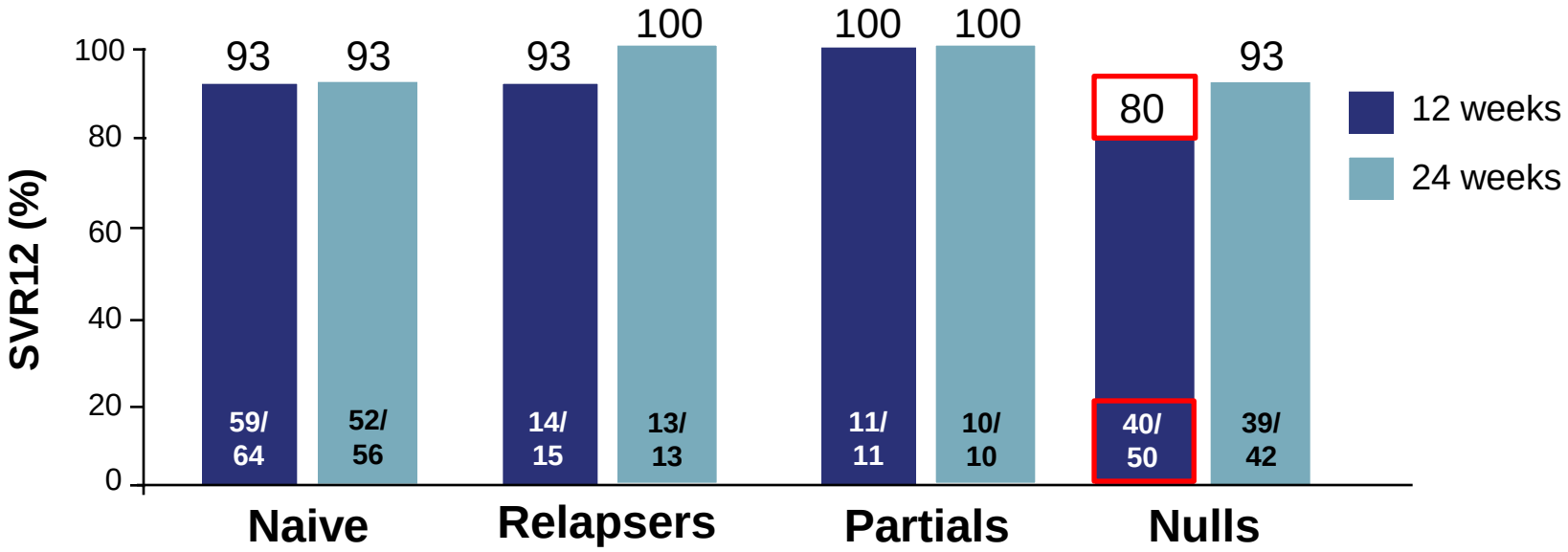
Ferenci CROI 2014

3D + RBV in Cirrhosis by GT 1 Subtype



Poordad EASL 2014, LB, *NEJM* 2014

GT 1a Null Cirrhotics Likely Need 24 Weeks



- Suggests that 24 weeks optimal for GT 1a null cirrhotics
- 12 weeks adequate for all others

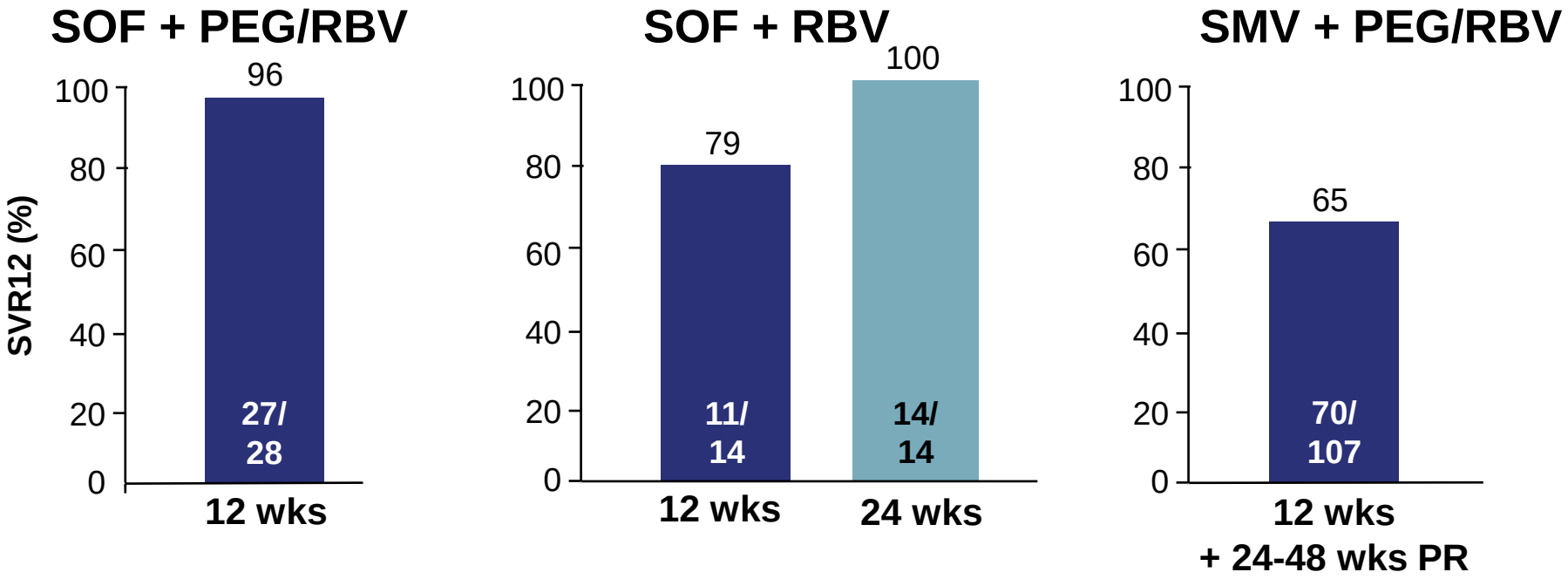
Poordad EASL 2014, LB, *NEJM* 2014

Summary of 3D Regimen + RBV

- Highly effective 12 week regimen
  - SVR 96% naïve/experienced
  - Similar GT 1a (95%) and GT 1b (98%)
- Large cirrhotic trial
  - Similar efficacy & safety
  - 12 weeks adequate for all but GT 1a nulls → 24 weeks
- Safety
  - Placebo controlled – minimal toxicity
  - Mostly to do with RBV – not needed for GT 1b

Treatment Options for GT 4 Infected Patients

Options for GT 4



- 3D +/- RBV – under study

Lawitz *NEJM* 2013, Ruane EASL 2014, Moreno EASL 2014

Treatment Options for GT 2 and GT 3 Patients

SOF+RBV: IFN Free Regimen Available for GT 2 and GT 3 Infected Patients

	Genotype 2 SOF + RBV 12 weeks N=73	Genotype 3 SOF + RBV 24 weeks N=250
Overall SVR	**93% (68/73)**	**84% (210/250)**
Outcome for subjects without SVR		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse	7% (5/73)	14% (34/249)
Treatment-naïve	3% (1/32)	5% (5/105)
Treatment-experienced	10% (4/41)	20% (29/144)
Other	0% (0/73)	2% (5/250)

SOVALDI full Prescribing Information. Gilead Sciences, Inc. December 2013.

Overall Summary

Summary

- One time testing of all baby boomers is essential
- Linkage to experts that can assess disease progression and treatment options
- Highly efficacious, short duration regimens with favorable safety profiles are now available
- Additional treatment options expected in the next 6 months
- Rapidly evolving field…

IDSA/AASLD Guidance Document Remains Current

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American Association for the Study of Liver Diseases

AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA

Infectious Diseases Society of America

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HCV Guidance

Wednesday, January 29, 2014

The Recommendations for Testing, Managing, and Treating Hepatitis C are now available.

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Official Press Release

Wednesday, January 29, 2014

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Read more >>

Background of the Hepatitis C Guidance

New direct-acting oral agents capable of curing hepatitis C virus (HCV) infection have been approved for use in the United States. The initial direct-acting agents were approved in 2011, and many more oral drugs are expected to be approved in the next few years. As new information is presented at scientific conferences and published in peer-reviewed journals, health care practitioners have expressed a need for a credible source of unbiased guidance on how best to treat their patients with HCV infection. To provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society-USA (IAS-USA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

New sections will be added, and the recommendations will be updated on a regular basis as new information becomes available. An ongoing summary of "recent changes" will also be available for readers who want to be directed to

Healthcare Reform: Quality Measures and the Impact on Practices

What is Quality?

- **Quality care is <u>safe, effective, patient centered, timely, efficient, and equitable</u>**

Committee on the *Quality of Health Care in America. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: National Academy Press*; 2001.

National Quality Agenda

- Better care
- Better health
- Lower costs through improvement
  - Looking at quality through an economic lens will lead to results when it is measured appropriately and accurately

Quality Priorities

- Making care safer by reducing harm caused in the delivery of care
- Engaging patients in their care
- Promoting effective communication and coordination of care
- Effective prevention and treatment practices
- Enable healthy living
- Making quality care more affordable through new health care delivery models

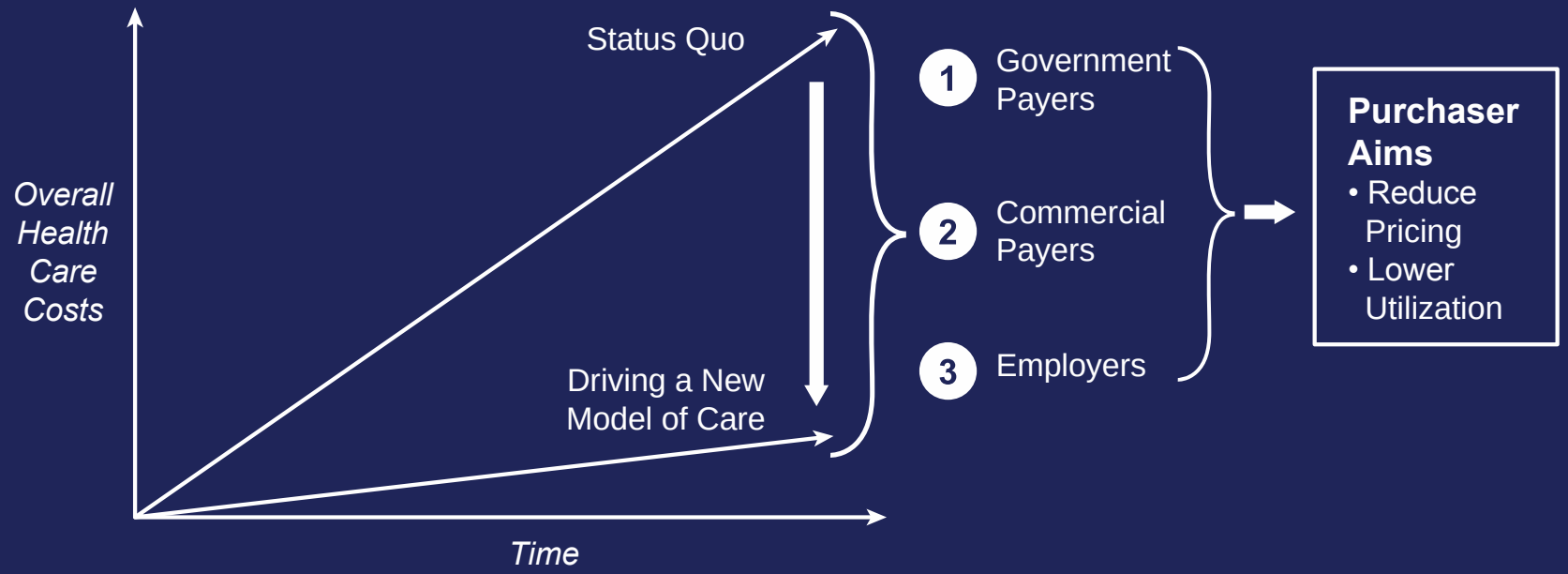
Why Quality Reporting?

- Healthcare is moving from a performance- to outcomes-based environment
- Reimbursement will be driven by measurement of value and quality

Value and Quality

- Focus on Patient Value
  - Value = Quality per unit cost over time
  - Improve quality, safety, efficiency, value of care
  - Control cost of care
  - Improve care coordination
- The future lies in cooperation, interaction and transparency around organized, personalized care

Value-Based Purchasers Seeking Lower-Cost Health Care



Defined Benefit Health Insurance Plan

Employers cost shift premiums to employees and adopt higher deductible plans.

	2012 (Pre-exchanges)	2013
PPO	70%	47%
HMO	18%	14%
CDHP*	12%	39%

*Consumer Directed Health Plan

Defined Contribution Health Insurance Plan

- Employers provide all their employees with monetary support to buy coverage on private exchanges
- Accenture study predicts 40 million employees covered by 2018 with a defined contribution plan

Sculpted Networks

- Insurances and large employers will contract directly with providers at transparent reference prices to pay a set amount for procedures or episodes of care

Payment Issues

- Narrow networks
- Bundled payments
- Episodes of care (Providers paid to treat a specific condition over a set period of time)
- High deductible health plans (Require collection at time of service)

Texas Care Alliance (TCA)

Nine regional health systems throughout the state to form the Texas Care Alliance (TCA), which seeks to pool patient and administrative data for large scale analysis that is expected to result in lower health care costs for the large companies the TCA targets. Those companies typically fund their own insurance plans.

The Move to Integrated Health Care Systems

- Healthcare is being directed toward Integrated Health Care Systems
- Healthcare providers are going to have to interpret what this push means to their individual practices and how they will continue to fit into the equation

Integrated Healthcare

"There is no evidence that one organizational structure delivers better care than others. What matters are an organization's internal capabilities and market environment, including the presence of strong leadership and organizational culture; clear purpose and shared goals; the sharing of data to help providers reach these goals; performance feedback and accountability for individual providers; participation in external quality improvement incentive programs; advanced care coordination capabilities and the use of coordinated chronic care teams; the use of recommended care management processes for the treatment of chronic illnesses; robust health information technology infrastructure; provider acceptance and use of evidence-based guidelines; and strong market incentives to improve value."

Integrated Healthcare Association: Lessons for the National Debate on Delivery System Reform

Hospital – Physician Relationships

A range of relationships exist between physician organizations and hospitals. Alignment of incentives between physician organizations and hospitals offer important opportunities for performance improvements across the entire continuum of care.

Compensation methodologies have played a key role in shaping hospital-physician organization relationships in California; in the absence of joint financial incentives, it is difficult to create alignment between hospitals and the physician organizations that use their services. Closer alignment between physician organizations and hospitals is critical, as a physician organization-centric model cannot bring about the institutional operational changes that will be needed to control overall costs. Hospitals are the highest-cost element of the delivery system, thus including them in initiatives to control costs and increase value is essential.

Accountable Care Organizations (ACOs)

ACOs are not a panacea for health care spending control. Higher-cost and inefficient providers have not faced enrollment penalties because the current market does not incentivize purchasers or consumers to choose lower-cost or more cost-efficient providers. As ACOs are rolled out across the country, health insurance benefit designs should reward patients for choosing higher-value ACOs, which will necessitate that cost and quality data are available and that consumer cost sharing is higher for less efficient providers.

Example of Successful Outcomes Based Reimbursement

- On July 3rd, 2014 the American Society of Clinical Oncology published a study showing that an experimental physician-payment method was found to have lowered costs by more than a third for caring for patients with three types of cancers
- The pilot (launched in 2009), involved five medical oncology groups collaborating with United Healthcare, and, "used an episode payment model, which reimbursed physicians on a fixed-price, **based on episodes of best-practices and patient outcomes**"
- By December of 2012, "use of this model for treatment of breast, lung, and colon cancers in 810 patients led to savings of more than $33 million when compared to anticipated costs"

Here Comes the VM

- The value-based modifier (VM) assesses both quality of care furnished and the cost of that care under the Medicare Physician Fee Schedule
- Begin phase-in of VM in 2015, phase-in complete by 2017
- For 2015, apply VM to physician payment in groups of 100+ eligible professionals (EPs)
- Performance period for 2015 VM is calendar year 2013, so the VM 2013 penalty will hit in 2015 like the 2013 PQRS penalty

VM Requirements

- Groups with 100+ EPs MUST select one of the following PQRS quality reporting mechanisms to avoid the -1.0% VM adjustment

PQRS Reporting Mechanism	Type of Measure
1. GPRO Web Interface	Measures focus on preventive care and care for chronic diseases (aligns with the Shared Savings Program)
2. GPRO using CMS-qualified registries	Groups select the quality measures that they will report through a PQRS-qualified registry
3. Administrative Claims Option	Measures focus on preventive care and care for chronic diseases (calculated by CMS from

Physician Quality Reporting System (PQRS)

- Started in 2007
- CMS program to report quality
- “By reporting PQRS quality measures, providers can quantify how often they are meeting a particular quality metric. Using the feedback report provided by CMS, eligible health care professionals (EPs) can compare their performance on a given measure with their peers” - www.cms.gov
- PQRS has been using incentive payments, and will begin to use payment adjustments in 2015 to encourage EPs to report on specific quality measures
- Quality reporting for these measures span **6 National Quality Standard (NQS) Domains**

NQS Domains (All PQRS Quality Measures Fall Under These 6 Domains)

1. ***Person and Caregiver-Centered Experience Outcomes***

   Measures that reflect the potential to improve patient-centered care and the quality of care delivered to patients.

2. ***Patient Safety***

   Measures that reflect the safe delivery of clinical services in both hospital and ambulatory settings and include processes that would reduce harm to patients and reduce burden of illness.

3. ***Communication and Care Coordination***

   Measures that demonstrate appropriate and timely sharing of information and coordination of clinical and preventive services among health professionals in the care team and with patients, caregivers, and families to improve appropriate and timely patient and care team communication.

NQS Domains (continued)

4. *Community, Population and Public Health*

Measures that reflect the use of clinical and preventive services and achieve improvements in the health of the population served.

5. *Efficiency and Cost Reduction Use of Healthcare Resources*

Measures that reflect efforts to significantly improve outcomes and reduce errors.

6. *Effective Clinical Care*

Measures that reflect clinical care processes closely linked to outcomes based on evidence and practice guidelines.

- Examples of quality measures from effective clinical care on following slide.

Where to Start

- **Go to cms.gov and download:**
  - **2014 Physician Quality Reporting System (PQRS): Implementation Guide**
  - **http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/Index.html**
  - **2014 Physician Quality Reporting System (PQRS) Measures List**
- Choose 9 measures from the PQRS Measures List across 3 different NQS domains and report each measure for at least 50% of Medicare Part B patients seen during the reporting period
- Report these measures using 1 of 4 Reporting Options

Other Reporting Options for PQRS

- Medicare Part B Claims
  - Report QDCs listed in the individual measures you have selected on applicable Medicare Part B Claims. Measures are calculated by CMS after they are received via claims
- Qualified PQRS Registry
  - Choose a qualified registry (CMS has a list of these registries at their website) Group practices must also register under the Group Practice Reporting Option (GPRO). GPRO aligns with the Shared Savings Program
- Electronic Health Record (EHR) Reporting
  - Your EHR must be Certified EHR Technology (CEHRT) **OR** you may use a CEHRT Data Submission Vendor (DSV). Lists of CEHRT DSVs can be obtained at cms.gov
- Qualified Clinical Data Registry (our example was the AGA DHRP)
  - New to 2014 - Differs from the PQRS Registry in that it is not limited to the measures listed under the PQRS option. Data submitted to CMS via a QDCR covers quality measures across multiple payers and is not limited to Medicare beneficiaries

2014 PQRS Qualified Registries

CMS announced the entities that self-nominated to participate as a 2014 qualified registry. The 2014 qualified registry will be able to report quality measure data to CMS, on behalf of individual eligible professionals and Group Practice Reporting Organization (GPRO) group practices, for the 2014 PQRS program year.

CMS provides a table with all Qualified Registries with the information below listed for each.

Registry Name	Contact Information	Accepting New Clients	Individual Measures Supported	Measures Groups Supported	GPRO Supported	Participated in Prior Year Registry Program	Services Offered and Cost
Entity	• Contact Person • Website • Phone Number	Yes	Measure Number	• IBD • Hepatitis C • Preventative Care	Yes	Yes	• Comprehensive PQRS solutions • All practices (solo, group, large academic • Pricing – Average $300

Can be found at: http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/Downloads/2014QualifiedRegistries.pdf

PQRS: Example of Effective Clinical Care Domain – the HCV Measures Group

The Hepatitis C (chronic) Measures Group is comprised of the following

- **Measure 84:** RNA testing before initiating treatment
- **Measure 85:** HCV genotype prior to treatment
- **Measure 86:** Antiviral treatment prescribed
- **Measure 87:** HCV RNA testing at week 12 of treatment
- **Measure 89:** Counseling regarding risk of alcohol consumption
- **Measure 90:** counseling regarding use of contraception prior to anti-viral therapy
- **Measure 183:** hepatitis A vaccination in patients with HCV
- **Measure 184:** hepatitis B vaccination in patients with HCV

The Hepatitis C Measures Group may be reported via claims or registry

PQRS: The Inflammatory Bowel Disease (IBD) Measures Group is comprised of the following measures:

- **Measure 269:** IBD: Type, Anatomic Location and Activity All Documented
- **Measure 270:** IBD: Preventive Care: Corticosteroid Sparing Therapy
- **Measure 271:** IBD: Preventive Care: Corticosteroid Related Iatrogenic Injury – Bone Loss Assessment
- **Measure 272:** IBD: Preventive Care: Influenza Immunization
- **Measure 273:** IBD: Preventive Care: Pneumococcal Immunization
- **Measure 274:** IBD: Testing for Latent Tuberculosis (TB) Before Initiating Anti-TNF (Tumor Necrosis Factor)Therapy
- **Measure 275:** IBD: Assessment of Hepatitis B Virus (HBV) Status Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy
- **Measure 226:** Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention

The IBD measures can only be reported as a group via the registry reporting mechanism

PQRS: The Preventive Care Measures Group is comprised of the following measures:

- **Measure 39:** Screening or Therapy for Osteoporosis for Women Aged 65 Years and Older
- **Measure 48:** Urinary Incontinence: Assessment of Presence or Absence of Urinary Incontinence in Women Aged 65 Years and Older
- **Measure 110:** Preventive Care and Screening: Influenza Immunization
- **Measure 111:** Preventive Care and Screening: Pneumonia Vaccination for Patients 65 years and Older
- **Measure 112:** Preventive Care and Screening: Breast Cancer Screening
- **Measure 113:** Preventive Care and Screening: Colorectal Cancer Screening
- **Measure 128:** Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up
- **Measure 173:** Preventive Care and Screening: Unhealthy Alcohol Use – Screening
- **Measure 226:** Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention

The preventive care measures group may be reported via claims or registry

Why You Should Care = CMS 'Penalty Box'

Year	eRx	EMR	PQRS	Total Penalty
2012	-1.0%	No penalty	No penalty	-1.0%
2013	-1.5%	No penalty	No penalty	-1.5%
2014	-2.0%	No penalty	No penalty	-2.0%
2015	No penalty	-1.0%	-1.5%	-2.5%
2016	No penalty	-2.0%	-2.0%	-4.0%

ASC Quality Reporting (ASCQR) Measures

ASC Quality Codes 1-5: G Codes Reported on Claims

No adverse event	**G8907**	**No burn, no fall, no hospital, no wrong site/side/patient**
Patient Burn	G8908	Patient experienced a burn prior to discharge
Patient Burn	G8909	**No** burn
Patient Fall in ASC facility	G8910	Fell within center (Parking Lot NOT included)
Patient Fall in ASC facility	G8911	**No** fall
Wrong site, wrong side, wrong patient, wrong procedure, wrong implant	G8912	Patient documented to have experienced a wrong site, wrong side, wrong patient, wrong procedure or wrong implant event
Wrong site, wrong side, wrong patient, wrong procedure, wrong implant	G8913	Patient documented **not** to have experienced a wrong site, wrong side, wrong patient, wrong procedure or wrong implant event
Hospital Transfer/Admission	G8914	Patient documented to have experienced a hospital transfer or hospital admission upon discharge from ASC
Hospital Transfer/Admission	G8915	Patient documented **not** to have experienced a hospital transfer or hospital admission upon discharge from ASC
Timing of Prophylactic Antibiotic	G8916	Patient with preoperative order for IV antibiotic surgical site infection (SSI)

Key Notes:

G8907 is used when no untoward events occur, and is subsequently used on the majority of claims.

Patient falls in the parking lot DO NOT COUNT in regards to code G8910.

Patients who are admitted to a hospital AFTER discharge DO NOT COUNT in regards to code 8914.

ASCQR Measures 6-11 (Reported via Quality Net Secure Portal)

Number	Measures for CY 2016 Payment Year	Data Collection Period	Submission Period
ASC-6	Safe Surgery Checklist Use	January 1, 2014 – December 31, 2014	January 1 , 2015 – August 15, 2015
ASC-7	ASC Facility Volume Data on Selected ASC Surgical Procedures	January 1, 2014 – December 31, 2014	January 1 , 2015 – August 15, 2015
ASC-8	Influenza Vaccination Coverage among Healthcare Personnel	October 1, 2014 – March 31, 2015	To Be Determined†
ASC-9	Endoscopy/Polyp Surveillance: Appropriate Follow-Up Interval for Normal Colonoscopy in Average Risk Patients	April 1, 2014 – December 31, 2014	January 1 , 2015 – August 15, 2015
ASC-10	Endoscopy/Polyp Surveillance: Colonoscopy Interval for Patients with a History of Adenomatous Polyps – Avoidance of Inappropriate Use	April 1, 2014 – December 31, 2014	January 1 , 2015 – August 15, 2015
ASC-11	Cataracts: Improvement in Patient's Visual Function within 90 Days Following Cataract Surgery††	January 1, 2015 - December 31, 2015	To be Determined

Full list at: http://www.oqrsupport.com/media/tools/ASC_Measure_Reporting_Start_Dates_2016_040214_508.pdf

ASC – 6 : Safe Surgery Checklist

- The use of a checklist creates an expectation that organizations assess effective **communication** and **safe practices** during three perioperative periods:
  - Before induction of anesthesia
  - Before scope entry
  - Before patient leaves the endoscopy suite
- **Impact on Patient Safety:**
  - In pilot study, WHO Checklist was found to reduce the rate of postoperative complications and death by more than one-third

Haynes et al. *A Surgical Safety Checklist to Reduce Morbidity and Mortality in a Global Population. New England Journal of Medicine* 360:491-9. (2009)

New ASC Measures for 2014

- ASC-9: Appropriate Follow-up interval for normal colonoscopy in average risk patients
- ASC-10: Colonoscopy interval for patients with a history of adenomatous polyps – avoidance of inappropriate use

Proposed Measure ASC 12

- ASC–12: Facility Seven-Day Risk-Standardized Hospital Visit Rate after Outpatient Colonoscopy
  - The outcome measured will be all-cause, unplanned hospital visits (admissions, observation stays, and emergency department visits) within 7 days of an outpatient colonoscopy procedure

Conclusion: Adapt and Adopt or Face Monetary Loss

- Despite limited evidence, reporting of hospital quality data and performance based reimbursement have emerged as two of the most widely advocated strategies for accelerating quality improvement[1]
- Subsequent reform has produced hundreds of quality measures subject to penalties or incentives (PQRS alone has 281 quality measures). This is the beginning of the new norm in healthcare

1. P. K. Lindenauer, M.D., M.Sc., D. Remus, Ph.D., R.N., S. Roman, M.D., M.P.H., M. B. Rothberg, M.D., M.P.H., E. M. Benjamin, M.D., A. Ma, Ph.D., and D. W. Bratzler, D.O., M.P.H. "Public Reporting and Pay for Performance in Hospital Quality Improvement" *The New England Journal of Medicine* 2007;356:486-96