

The impact of the treatment of HCV in developing Hepatocellular Carcinoma

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Hepatocellular Carcinoma (HCC)

- Hepatocellular carcinoma is the 4th most common cancer in the world
- Third leading cause of cancer related death
- 80% of HCC is caused by chronic HCV or HBV infection
- HCC rarely seen during the first 4 decades of life,
 - except in populations in which HBV infection is hyperendemic.
- The mean ages of diagnosis with HCC were :
 - 55–59 years in China
 - 63–65 years in Europe and North America

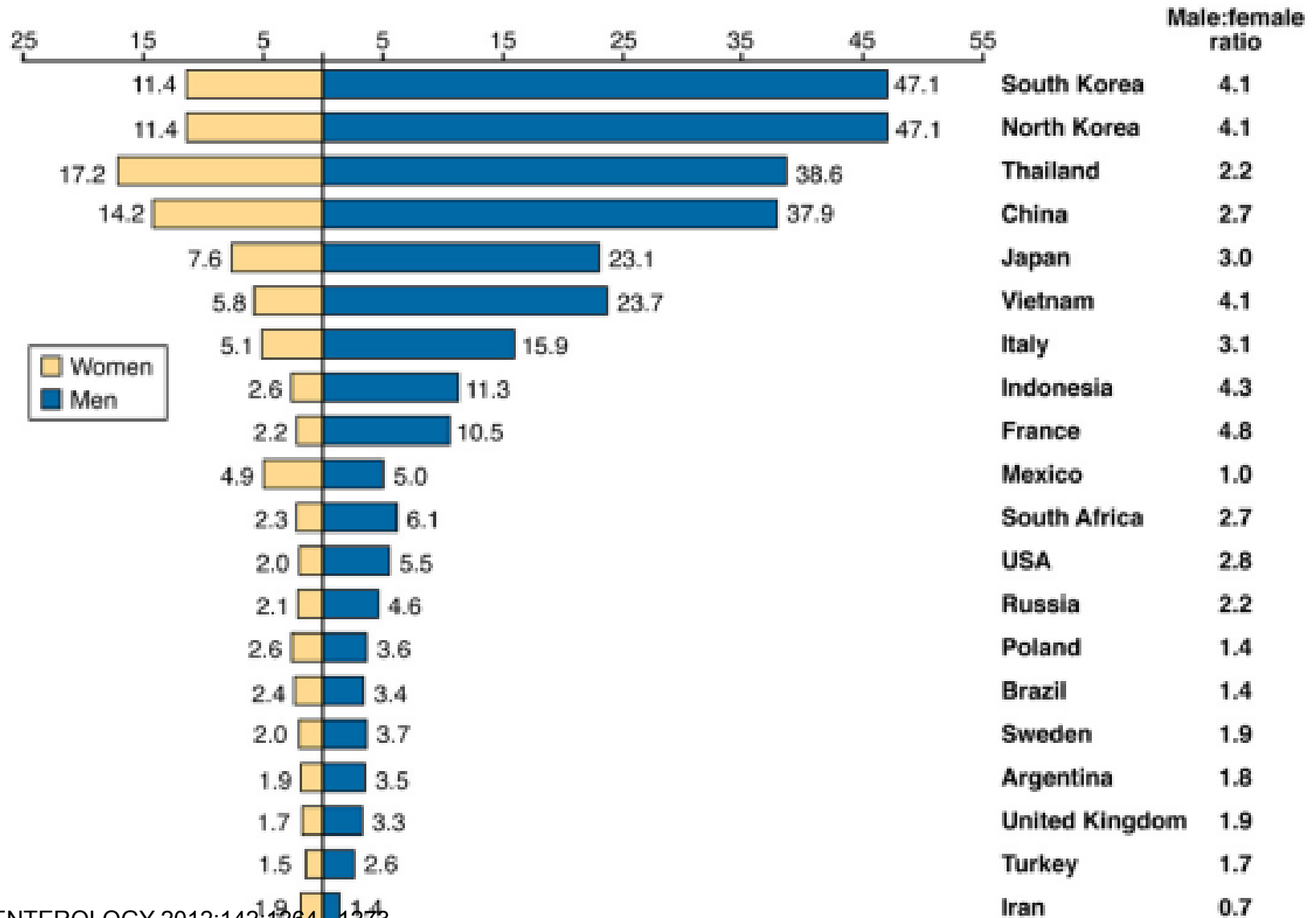
HCC and Hepatitis C

- Risk of HCC increases with fibrosis stage
- Most cases of HCV-related HCC occur among patients with advanced fibrosis/cirrhosis
- Incidence of cirrhosis 25–30 years after HCV infection is 15%–35%,
 - highest among recipients of HCV-contaminated blood products and hemophiliac patients
 - lowest among women who received dose of contaminated anti-D immunoglobulin
- HCC develops at annual rate of 1%–4%
 - rates up to 8% have been reported in Japan.

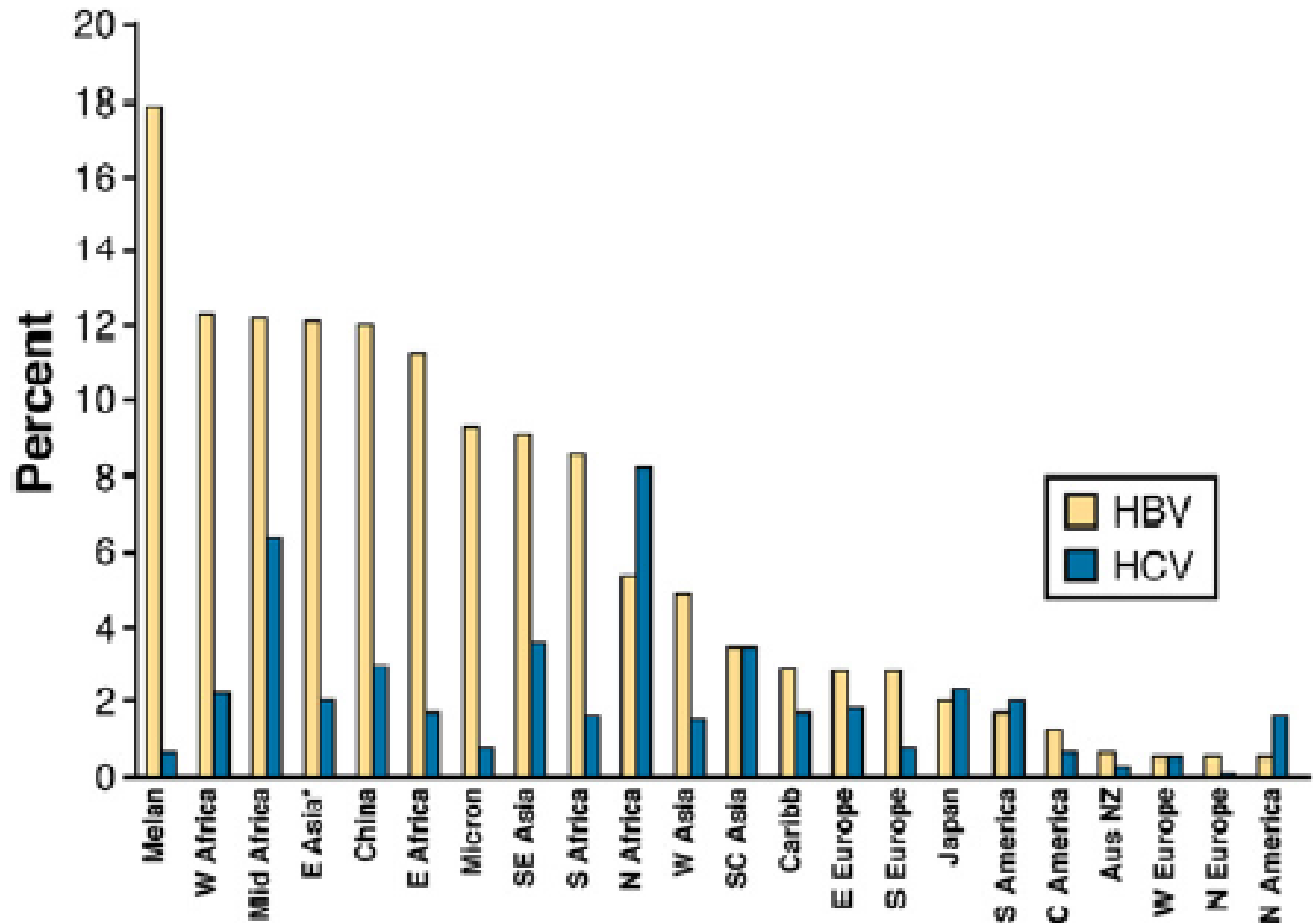
HCC and Hepatitis C: Other reported risk factors

- Gender
- Co-infection with HBV or HIV
- Diabetes, obesity, steatosis
- viral genotype (HCV 1b)
- Level of alcohol consumption
- Age
- Thrombocytopenia
- Increased levels of alpha -fetoprotein

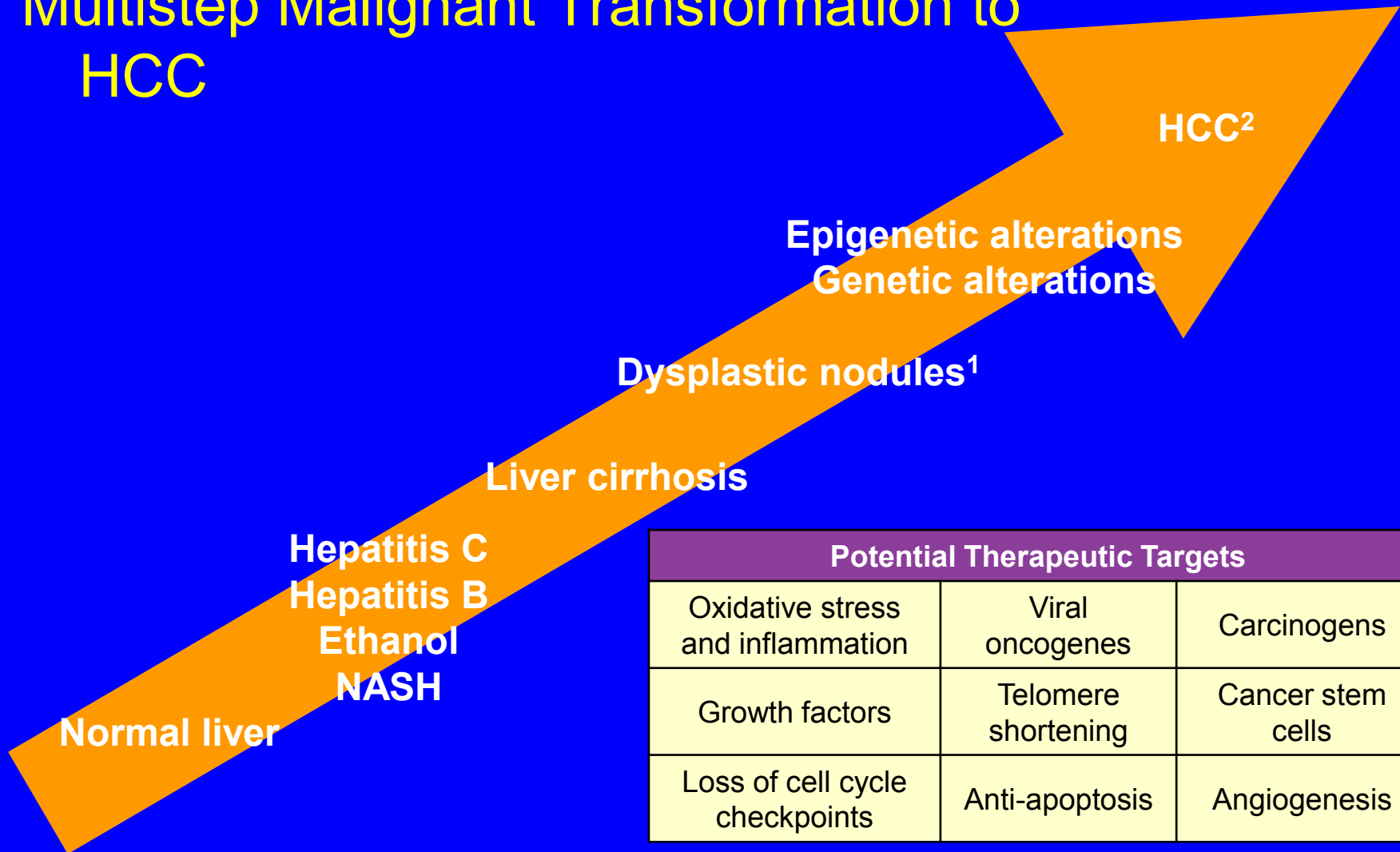
Age-standardized incidence rates of liver cancer per 100,000 person-years



Prevalence of HBsAg carrier and chronic HCV status in different geographic regions



Multistep Malignant Transformation to HCC



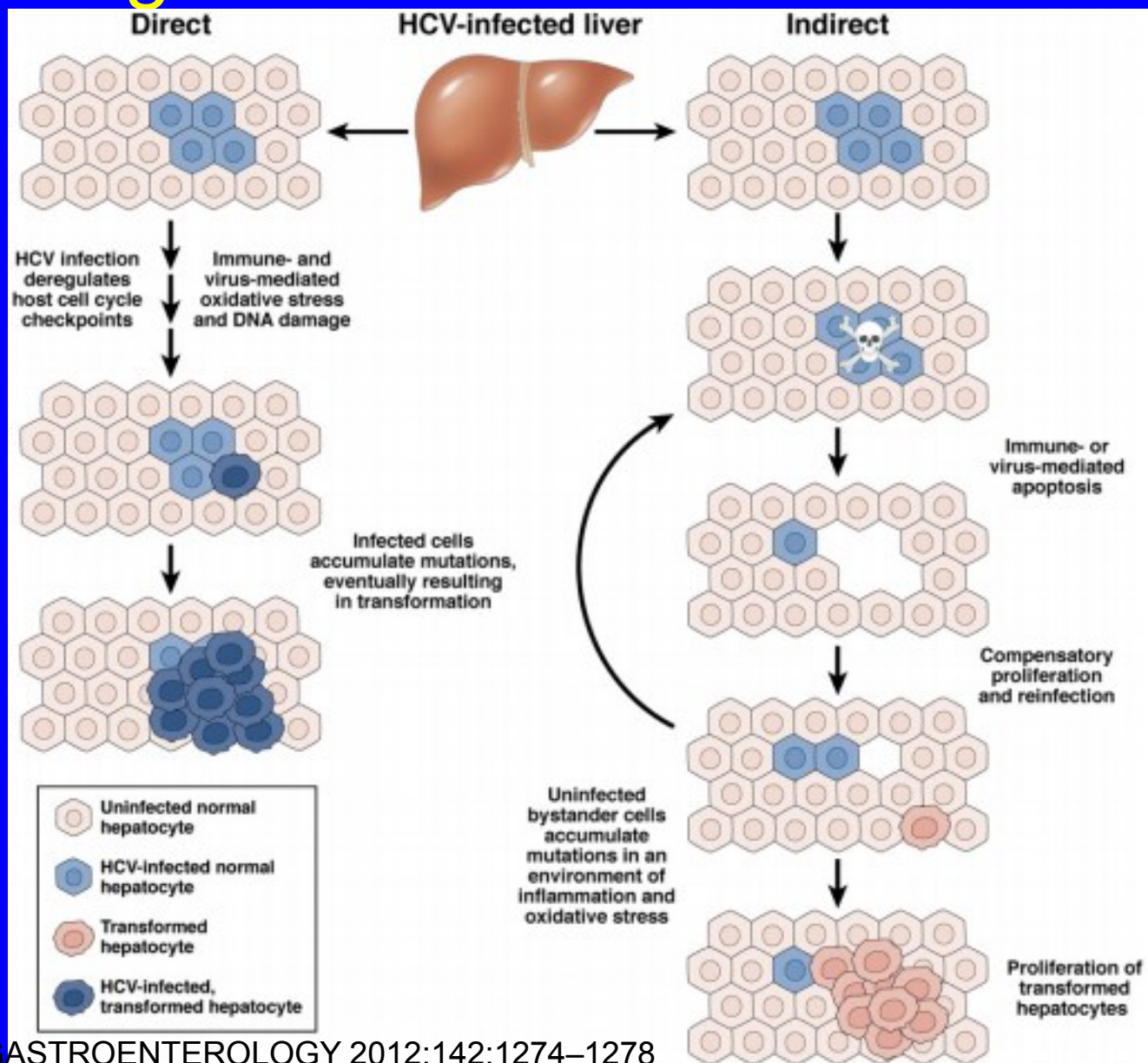
1. Tornillo L, et al. Lab Invest. 2002;82:547-553.

2. Verslype C, et al. AASLD 2007. Abstract 24.

Is Hepatitis C infection carcinogenic?

- Active HCV infection increases the risk of HCC by 18-fold
- 8% of HCC cases in HALT-C study had no cirrhosis
- Hepatitis C elicits inflammatory and fibrotic responses in the host contributing to carcinogenesis
- SVR reduces risk of HCC by 3 fold in cirrhotic patients

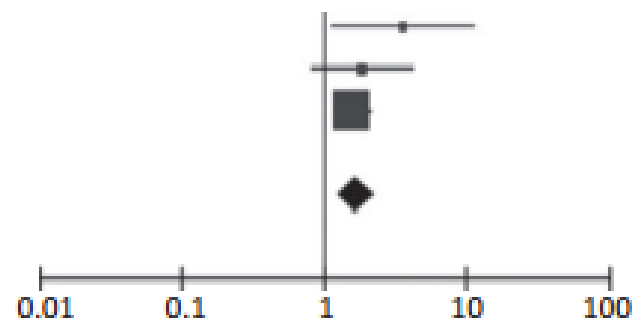
Direct vs indirect mechanisms of carcinogenesis in the HCV-infected liver



Cirrhosis regression in patients with and without a sustained viral response in trials in which the follow-up biopsy had a mean or median time of < 36-months

Number of Events/Total (%)

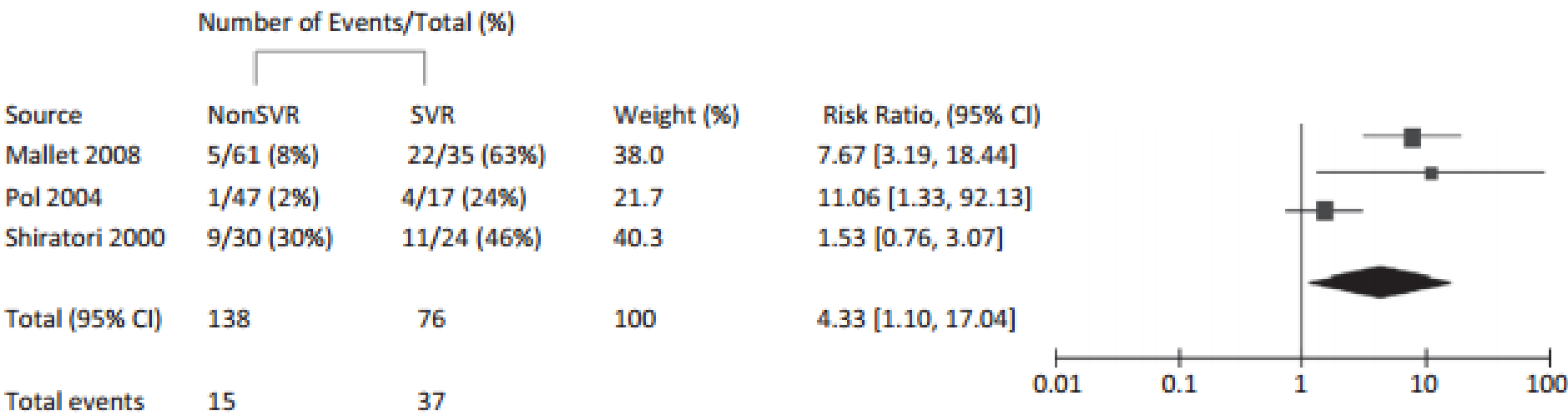
Source	NonSVR	SVR	Weight (%)	Risk Ratio, (95% CI)
Abergel 2004	4/43 (9%)	6/18 (33%)	6.8	3.58 [1.15, 11.20]
Arif 2003	4/9 (44%)	5/6 (83%)	13.2	1.88 [0.83, 4.23]
Poynard 2002	50/116 (43%)	25/37 (68%)	80.0	1.57 [1.15, 2.13]
Total (95% CI)	168	61	100	1.70 [1.26, 2.29]
Total events	58	36		



Test for Heterogeneity: $\text{Chi}^2 = 2.07$ ($P = 0.35$), $I^2 = 3\%$

Test for overall effect: $Z = 3.47$ ($P < 0.01$)

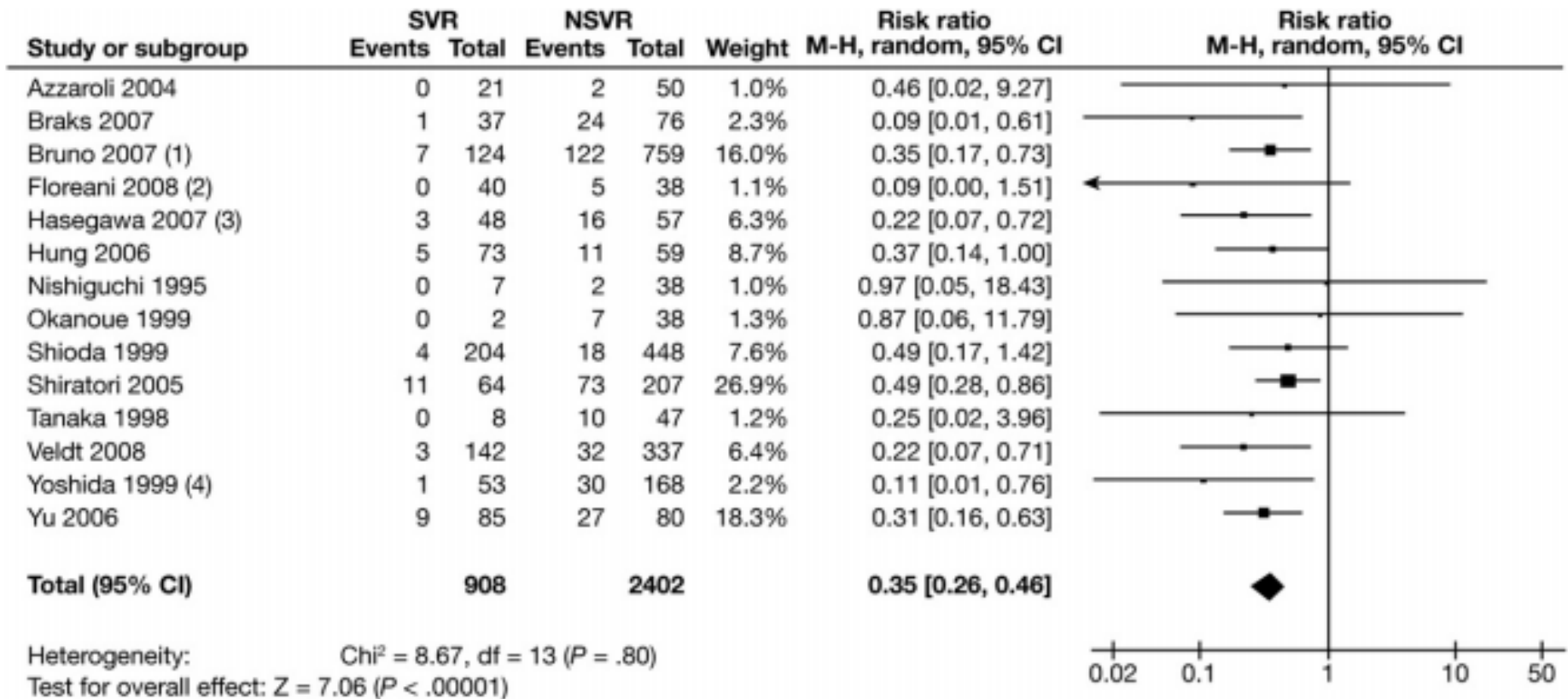
Cirrhosis regression in patients with and without a sustained viral response in trials in which the follow-up biopsy had a mean or median time of >36-months



Test for Heterogeneity: $\text{Chi}^2 = 9.95$ ($P < 0.01$), $I^2 = 80\%$

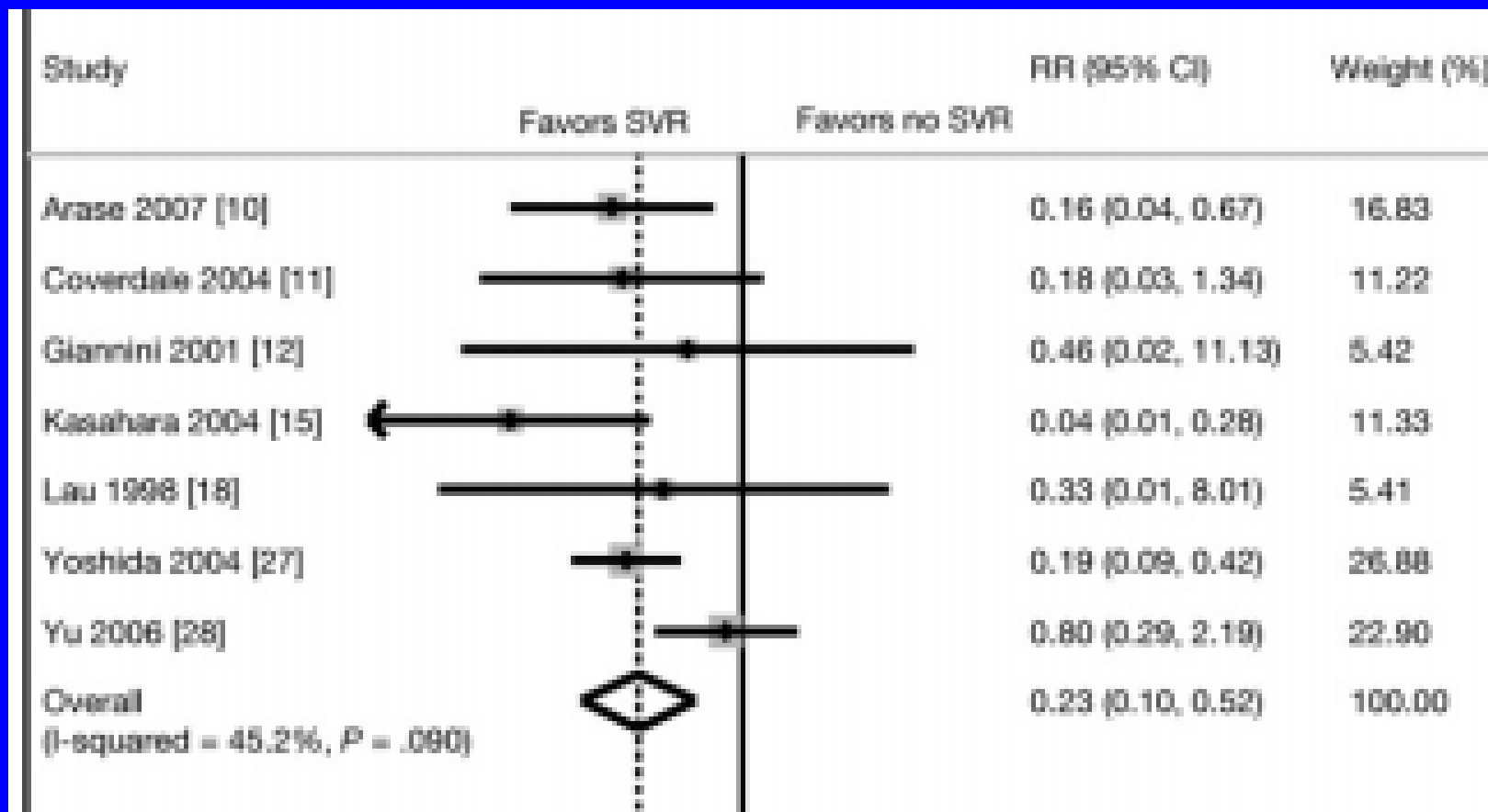
Test for overall effect: $Z = 2.10$ ($P = 0.04$)

Antiviral Therapy With SVR Reduces Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus–Related Cirrhosis

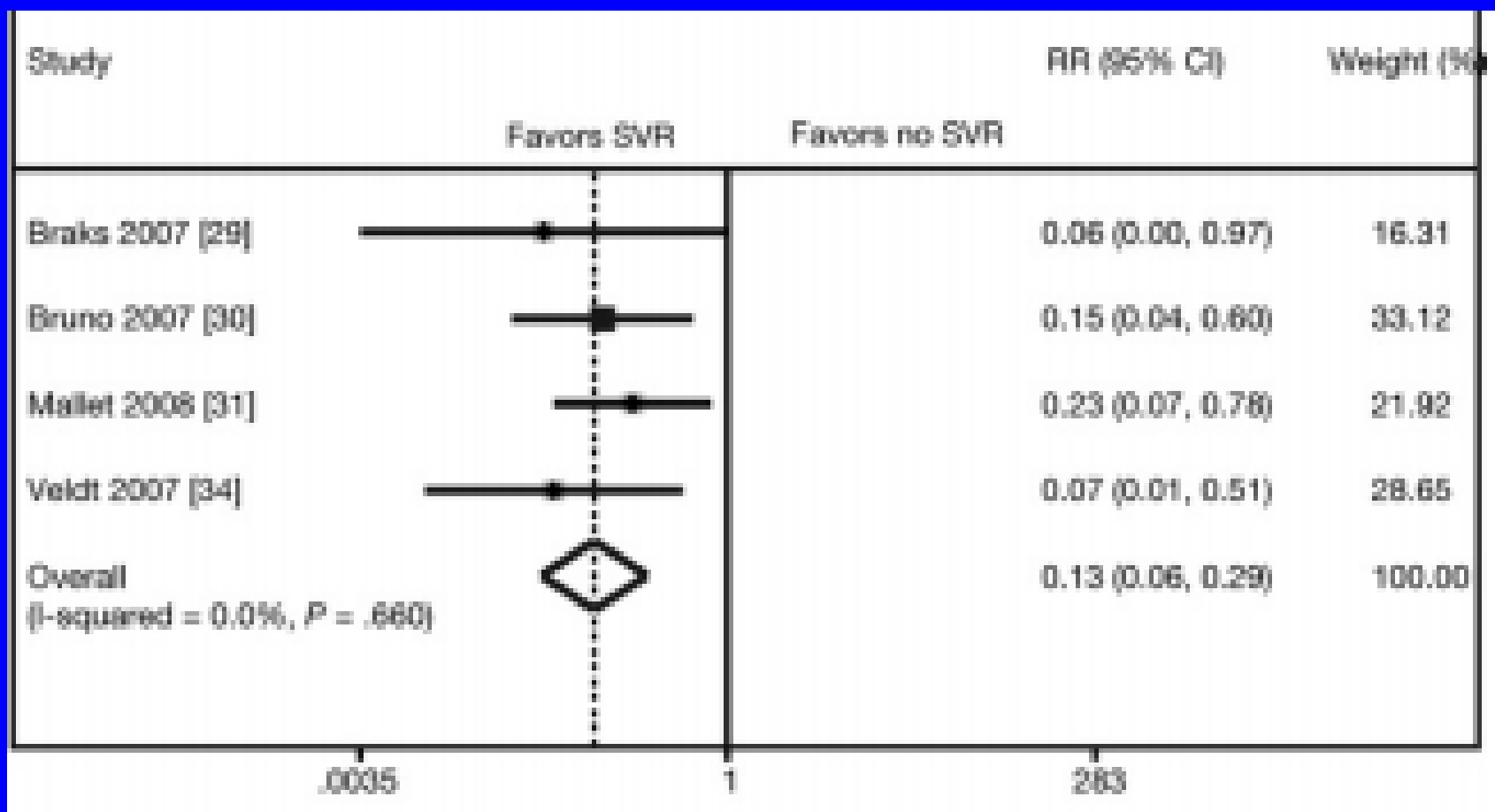


Maintenance interferon did not reduce risk of HCC

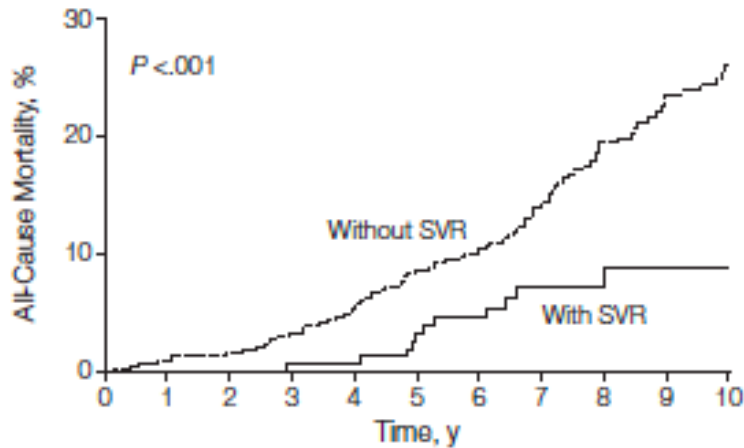
SVR reduces HCC risk across all fibrosis stages



SVR reduces HCC risk in those with cirrhosis

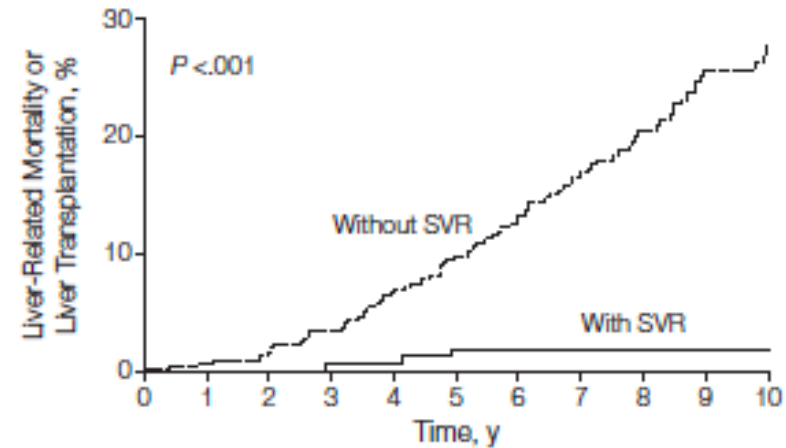


SVR Decreases but Does Not Eliminate Risk for Liver Related Complications in those with hepatitis C



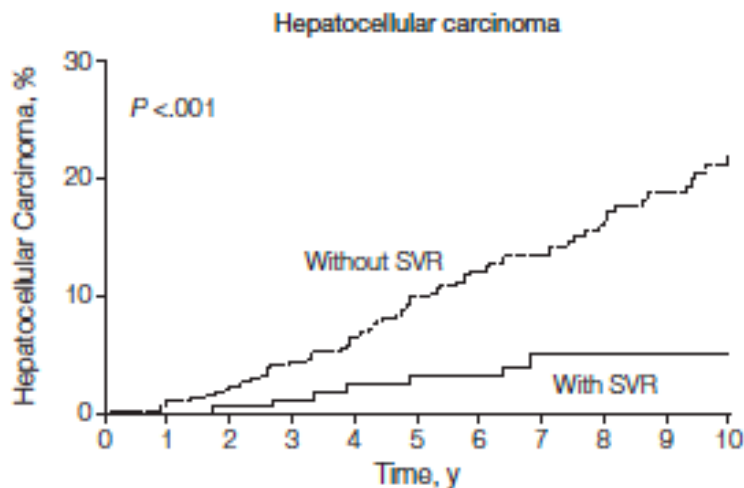
No. at risk

Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



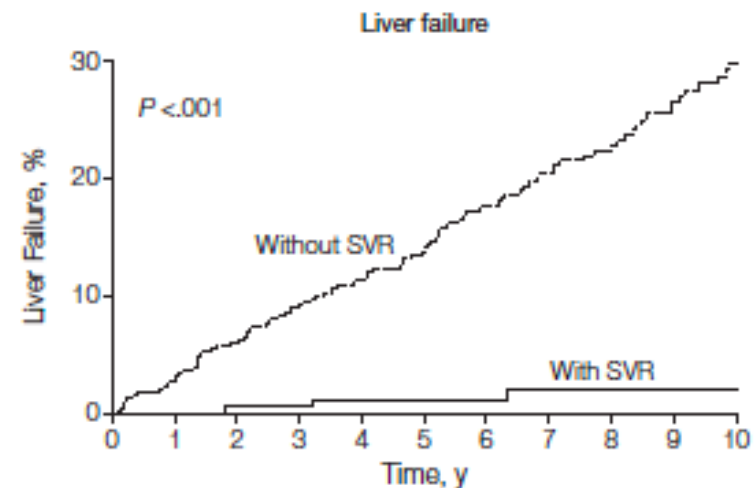
No. at risk

Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28



No. at risk

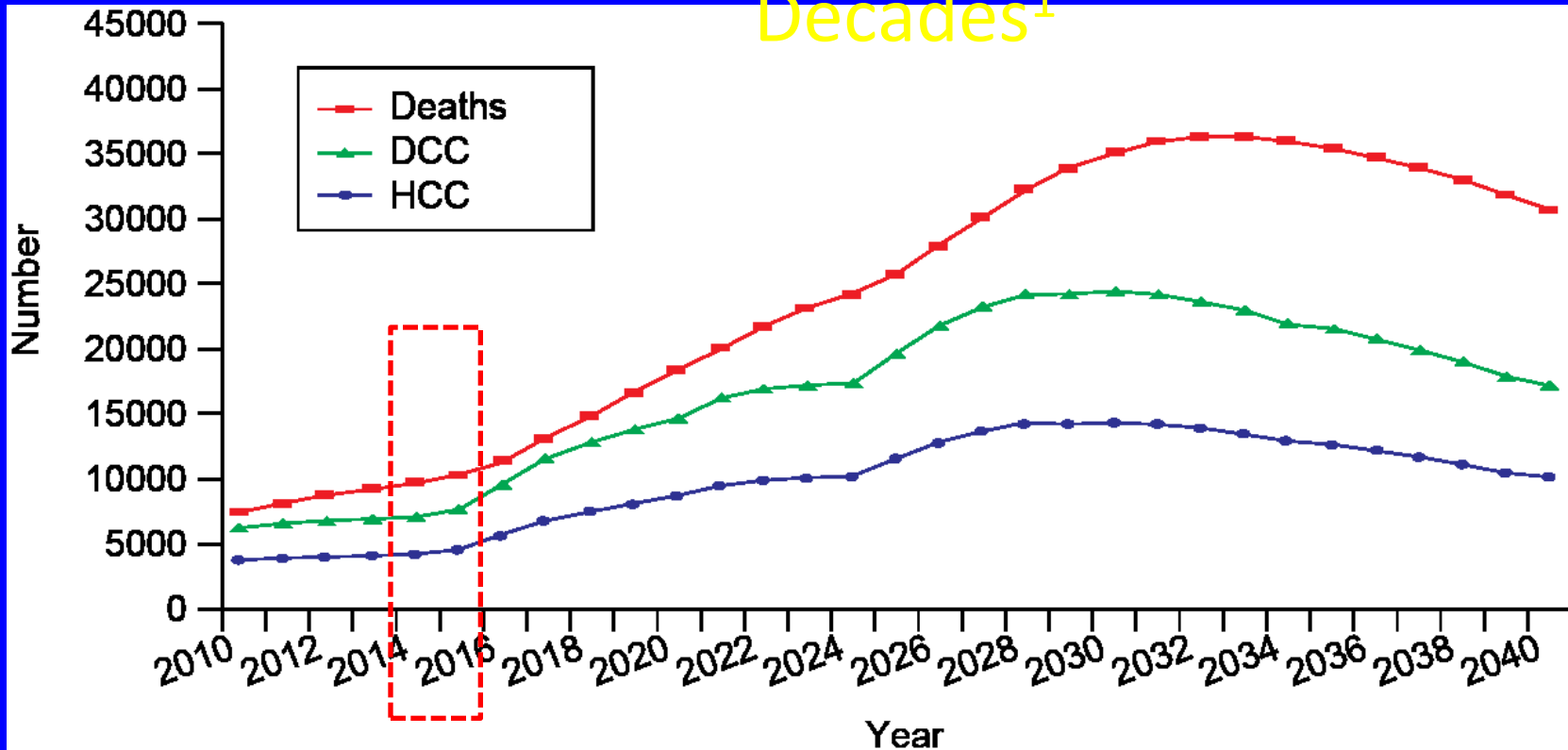
Without SVR	405	390	375	349	326	294	269	229	191	151	122
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No. at risk

Without SVR	405	384	361	337	314	288	259	216	184	143	113
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Projected Incidence of HCV Related Liver Cancer and Death Also Expected to Peak in Coming Decades¹



DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma

Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection²

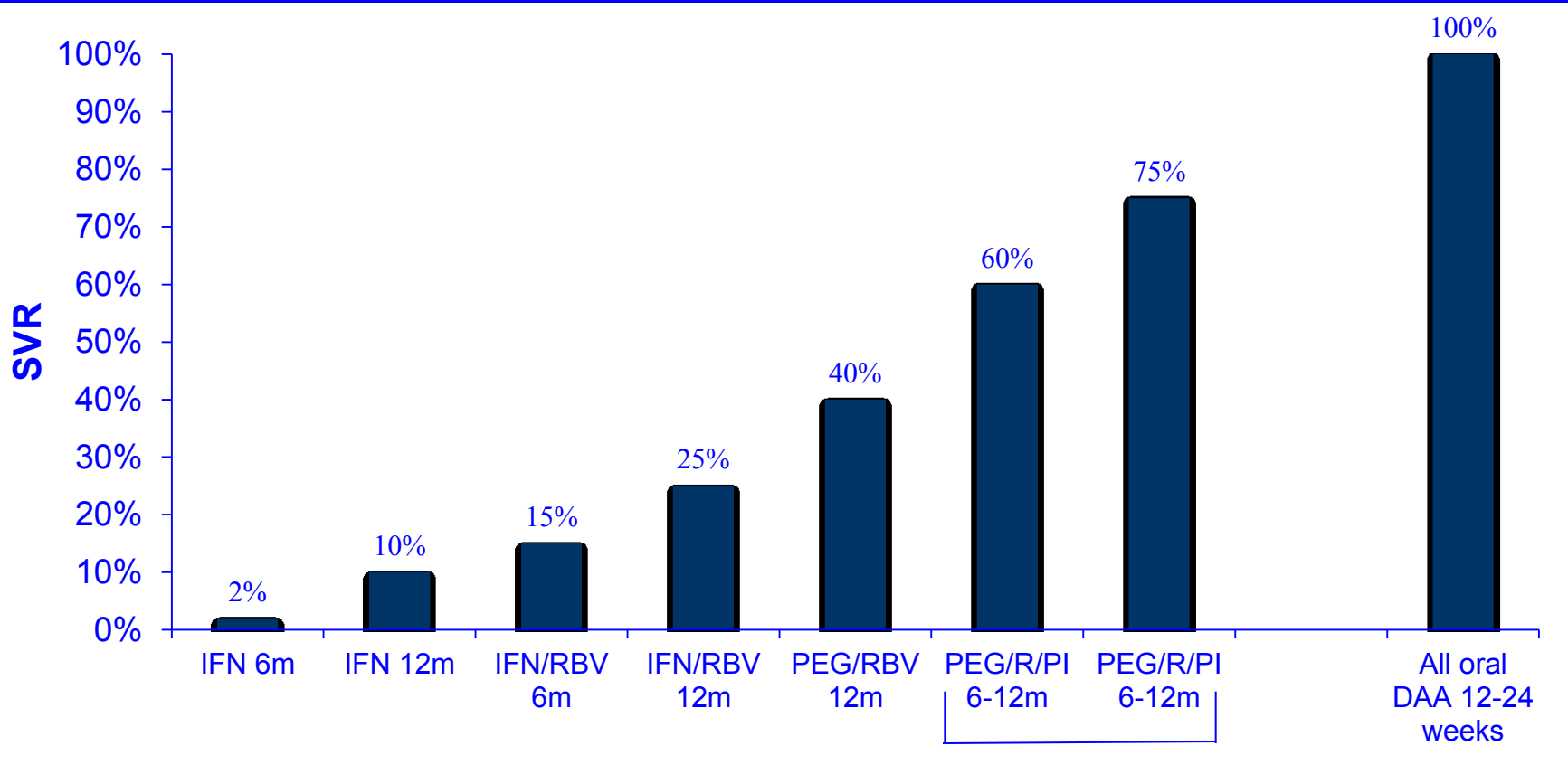
AASLD Surveillance Guidelines

- Surveillance recommended in at-risk groups
- HCC surveillance should be performed with ultrasound
- Patients should be screened at 6-mo intervals
 - AFP levels not part of surveillance guidelines

APASL Surveillance Guidelines

- Surveillance recommended in at-risk groups
- HCC surveillance should be performed with ultrasound
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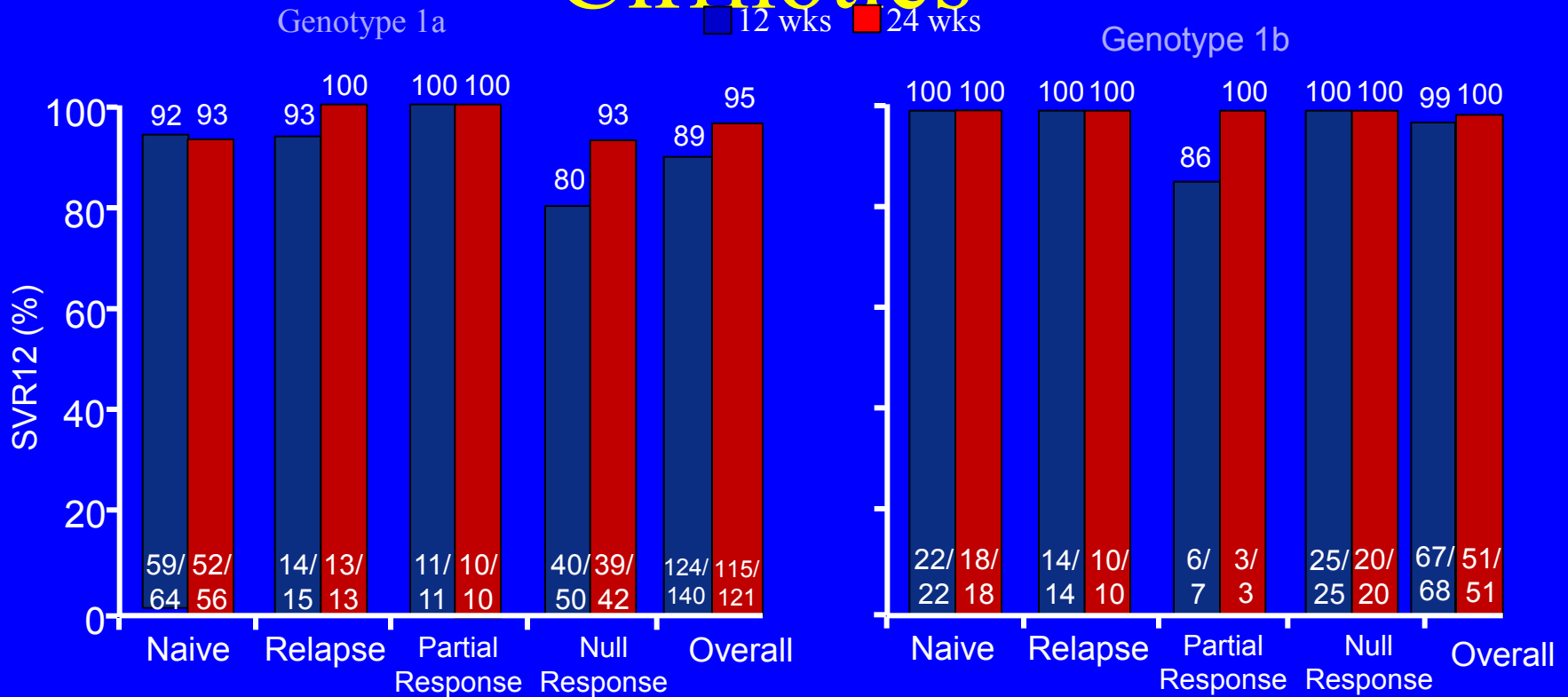
Evolution of Therapy in HCV GT1



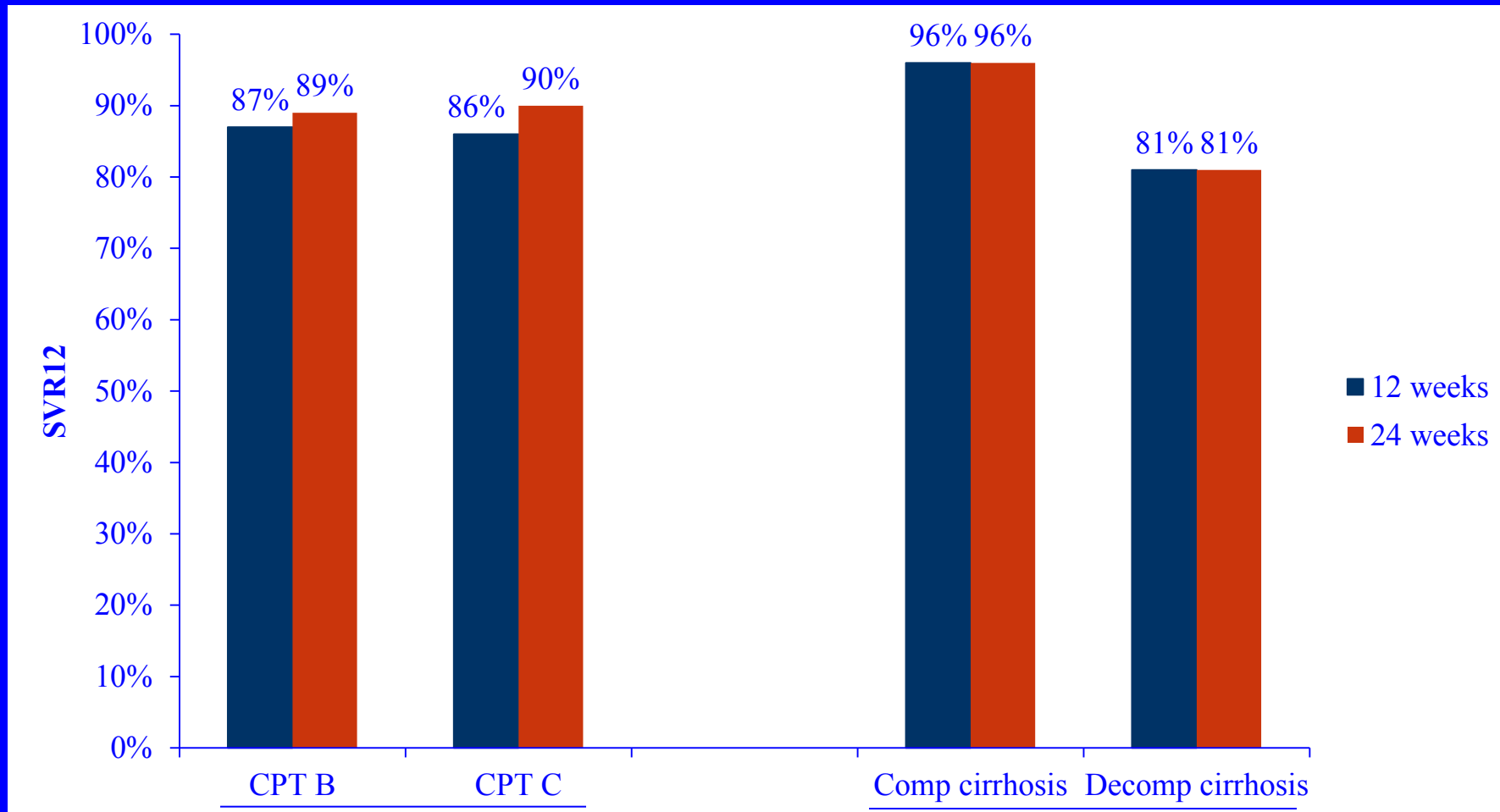
Genotype 3 requires additional strategies to achieve success of genotype 1

TURQUOISE II: 12 vs 24 Wks

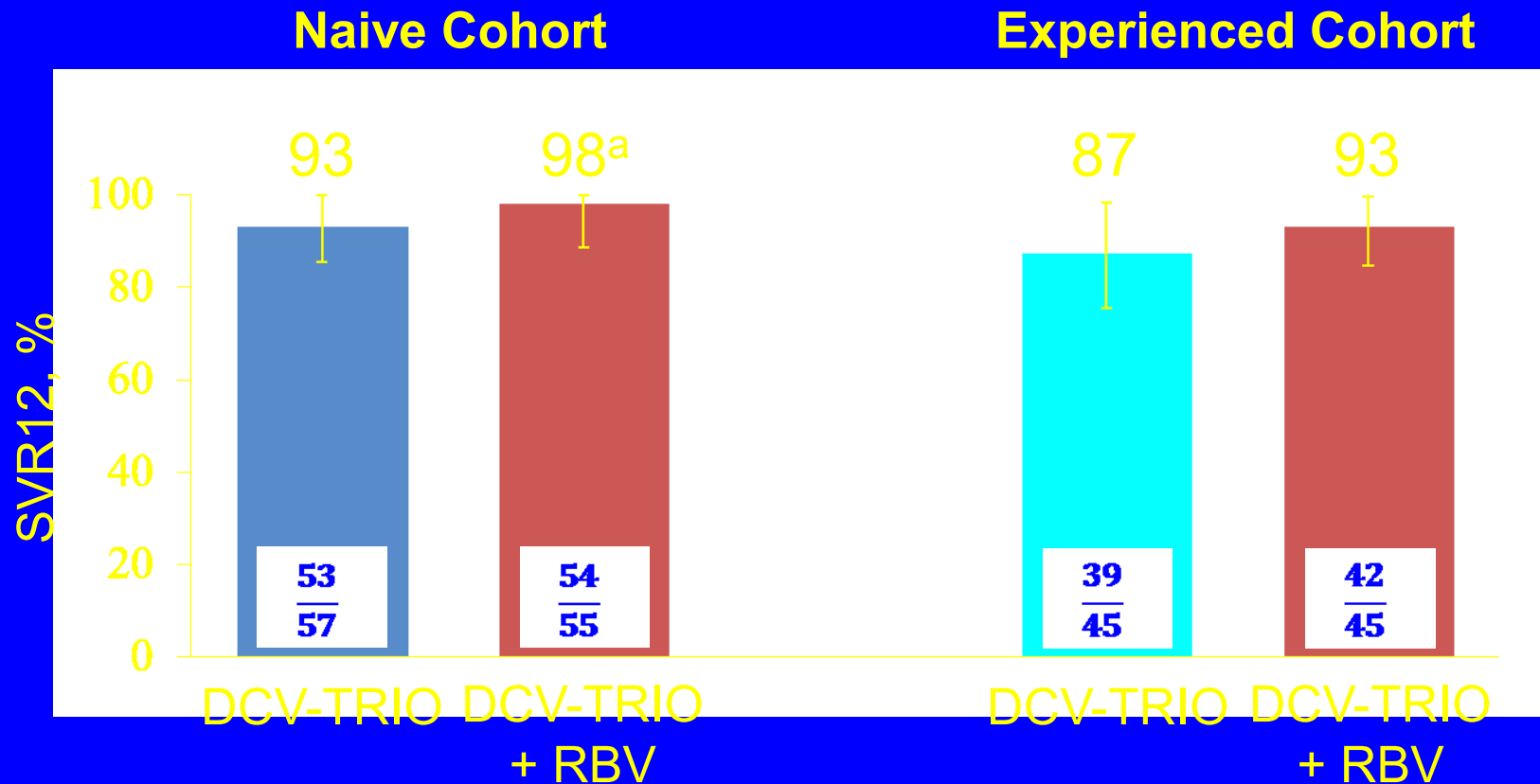
OMV/PTV/RTV + DSV + RBV in Cirrhotics



SOLAR: SVR12 in Patients With Advanced Liver Disease



Daclatasvir/Asunaprevir/Beclabuvir, ± Ribavirin for 12 weeks for G1



^aOne patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 97.5% confidence intervals.

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 (%/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

The Impact of HCV Treatments on HCC development

- We have the tools to achieve SVR in the majority of chronically infected hepatitis C patients
- These tools can reduce HCC development worldwide
- High SVR rates in F0-F4 fibrosis
- Those who are cured with cirrhosis must be entered into screening for HCC (US+AFP) if available
- Cirrhosis regression will occur in many who achieve SVR
- HCC risk will fall
 - Long term studies required to assess natural history of cirrhosis patients who achieve SVR on HCC development

The Impact of HCV Treatments on HCC development

