I NUOVI FARMACI PER HCV: FREQUENZA DELLA PATOLOGIA, EVIDENZE DI EFFICACIA E SICUREZZA, STRATEGIE DI GESTIONE

ISTITUTO SUPERIORE DI SANITÀ
CNESPS - Farmacoepidemiologia

La prognosi nel paziente con epatite C

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Hepatitis C

- Natural history
- Not only a liver disease
- A “curable” disease
- What HCV “cure” means…..

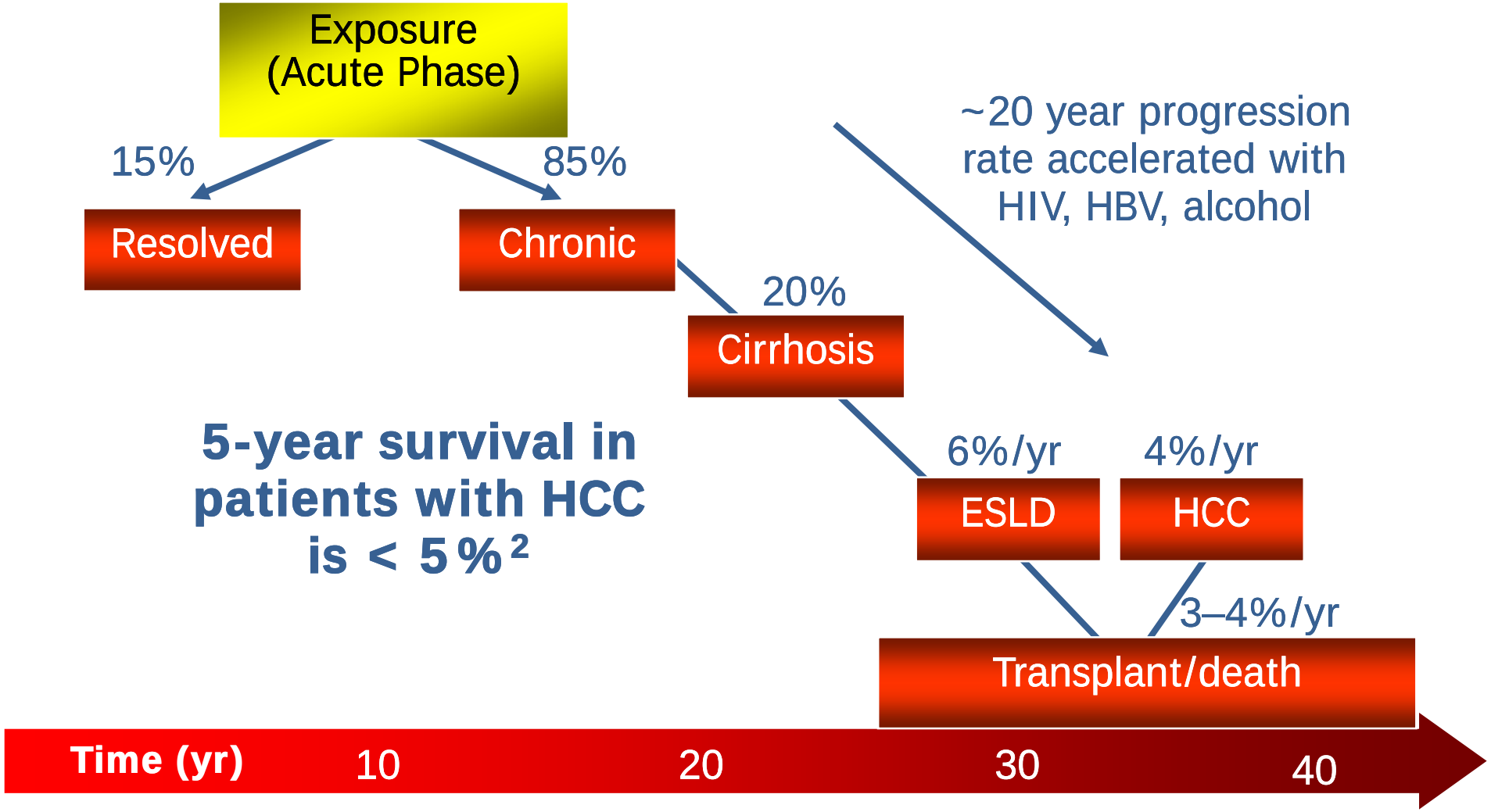
Epidemiology provides data for policy and action

	HIV[1]	HCV[2,3]	HBV[4]
Prevalence	34M	185M	400M
Incidence	2.5M	4M	?
Mortality	1.7M	0.35M	0.62M

4-5M coinfected patients,
depending on location and routes of transmission

[1]UNAIDS Global Report 2012; [2]HANAFIAH *et al,* Hepatology 2013
[3]PERZ *et al,* J Hepatol 2006; [4]GOLDSTEIN *et al,* Int J Epidemiol 2005

Natural History of HCV Infection



HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

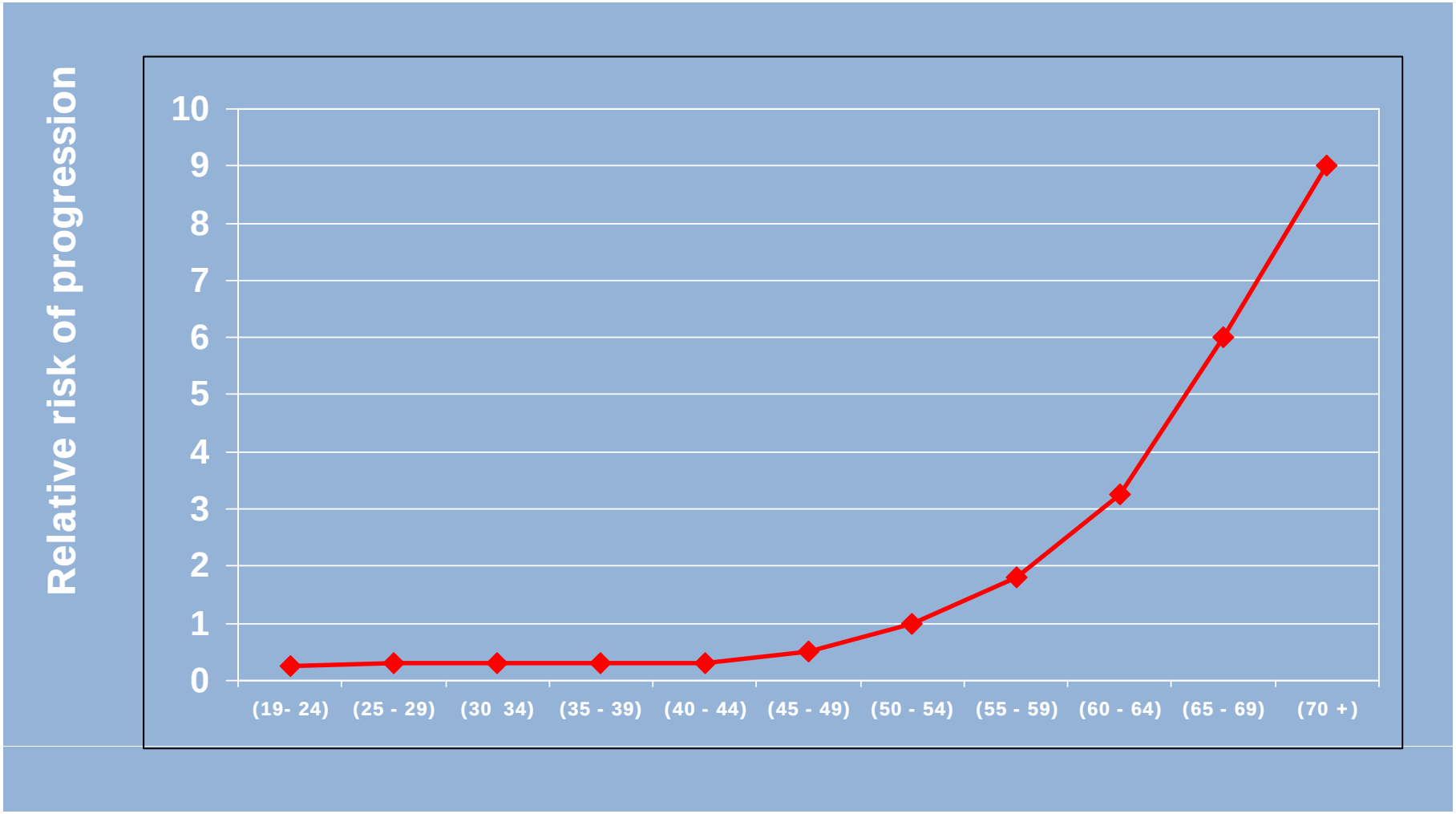
Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

Factors Associated with Advanced Fibrosis

Type of Factor	Well Established Factors
Host	• Age at infection • Duration of infection • Male gender • Baseline fibrosis
Viral	• HIV infection • HBV infection
External	• Heavy alcohol use

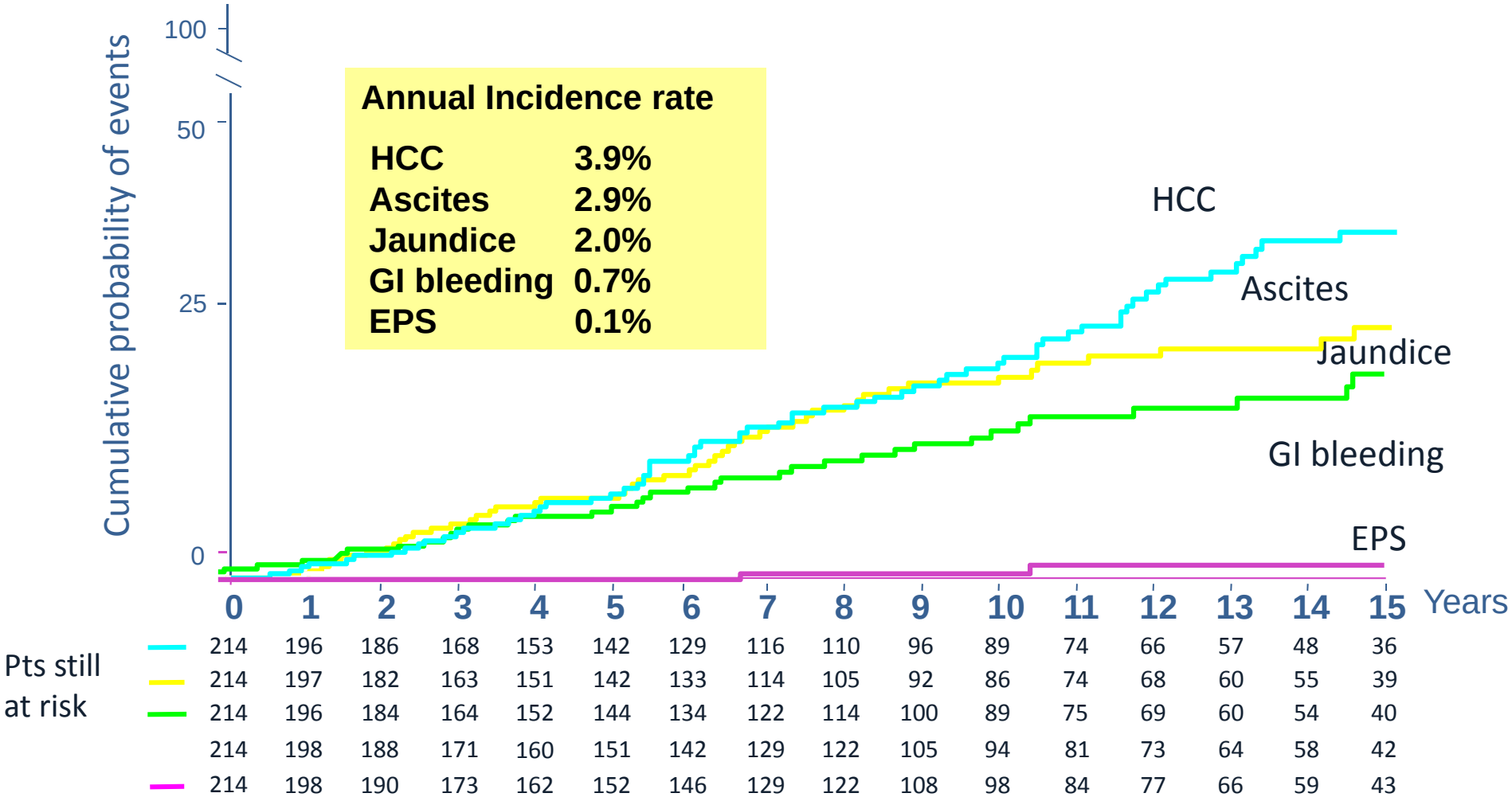
Bialek SR, et al. *Clin Liver Dis.* 2006;10:697-715.

Risk of Fibrosis Progression Increases with Age



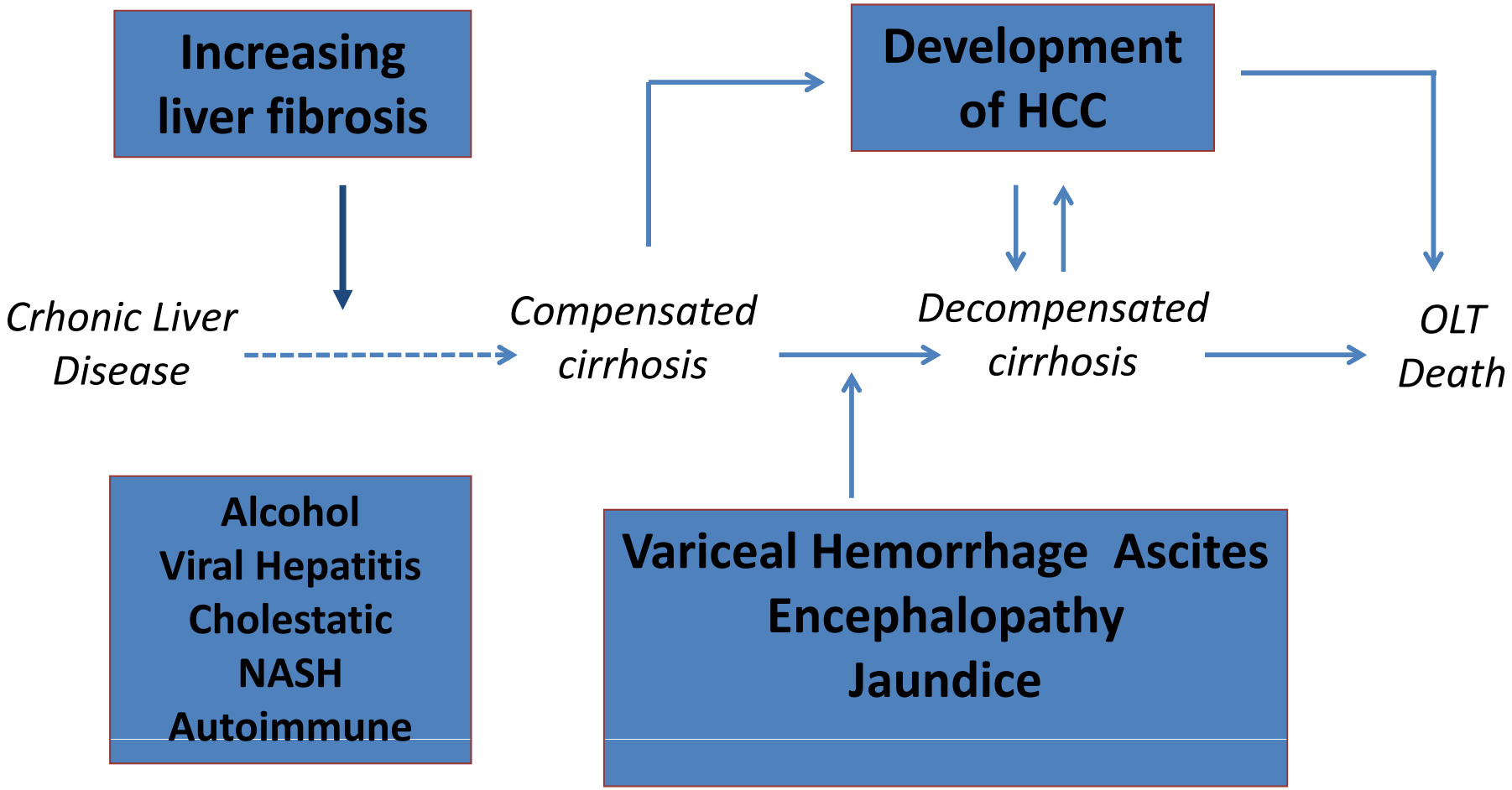
Ryder S et al. *Gut* .2004;53:451-55.

The long-term outcome of HCV compensated cirrhosis: a 17-yr follow-up of 214 Pts



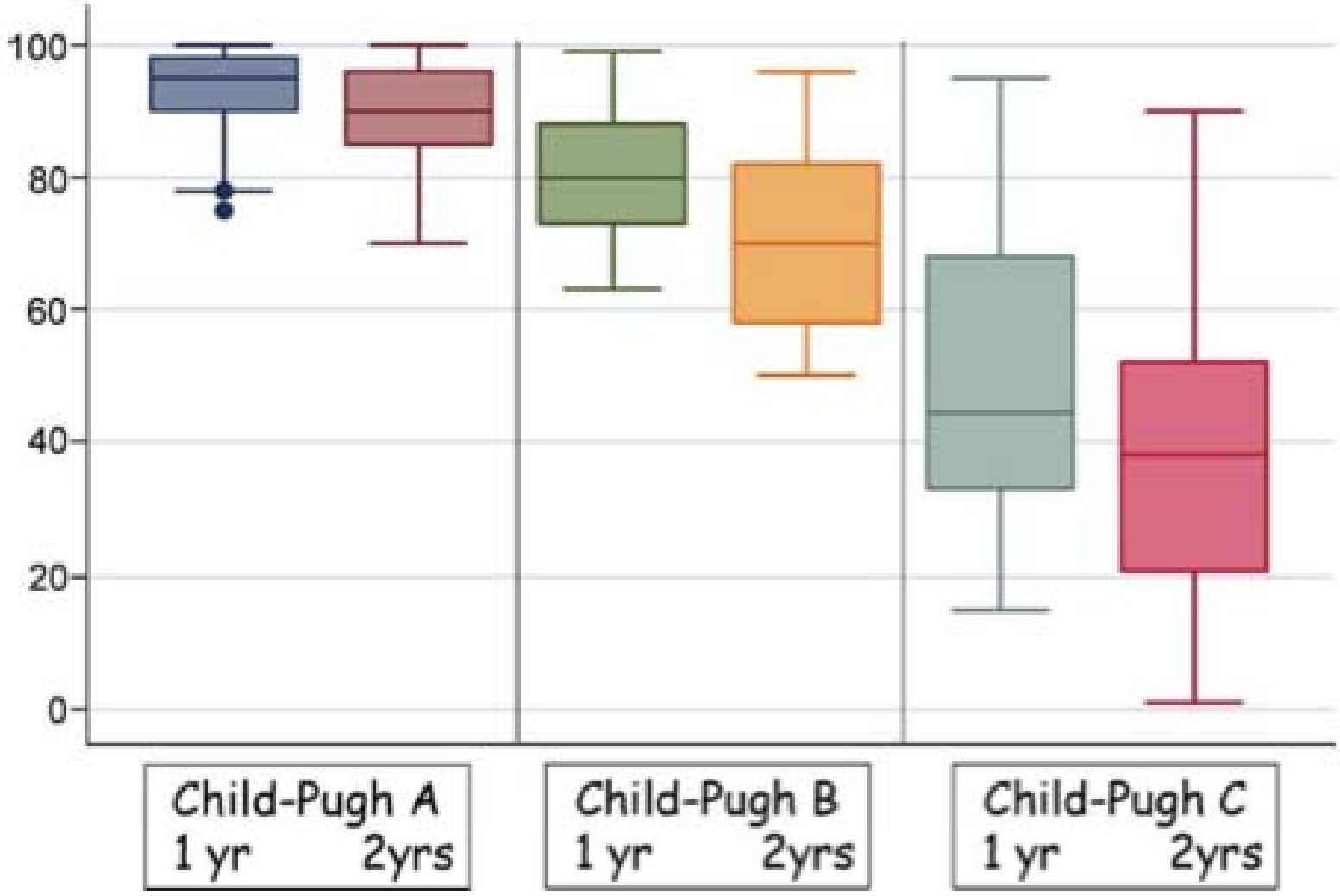
Sangiovanni A et al Hepatology 2006

The natural history of liver disease:
a simplified view



Garcia-Tsao, 2008

Box plots of one and two-year survival rates in Child–Pugh class A, B and C



(D'Amico G et al, J Hepatol 06)

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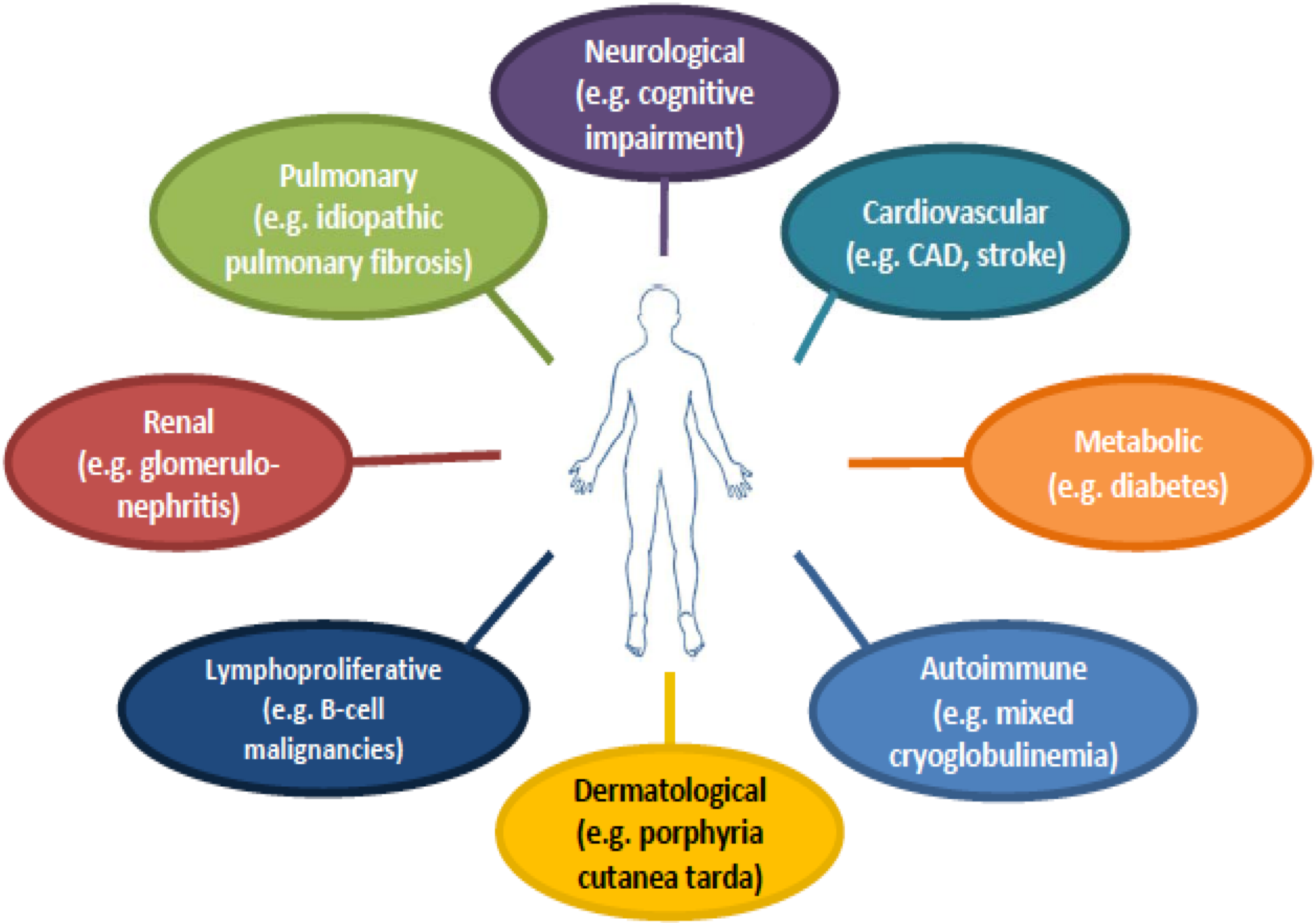
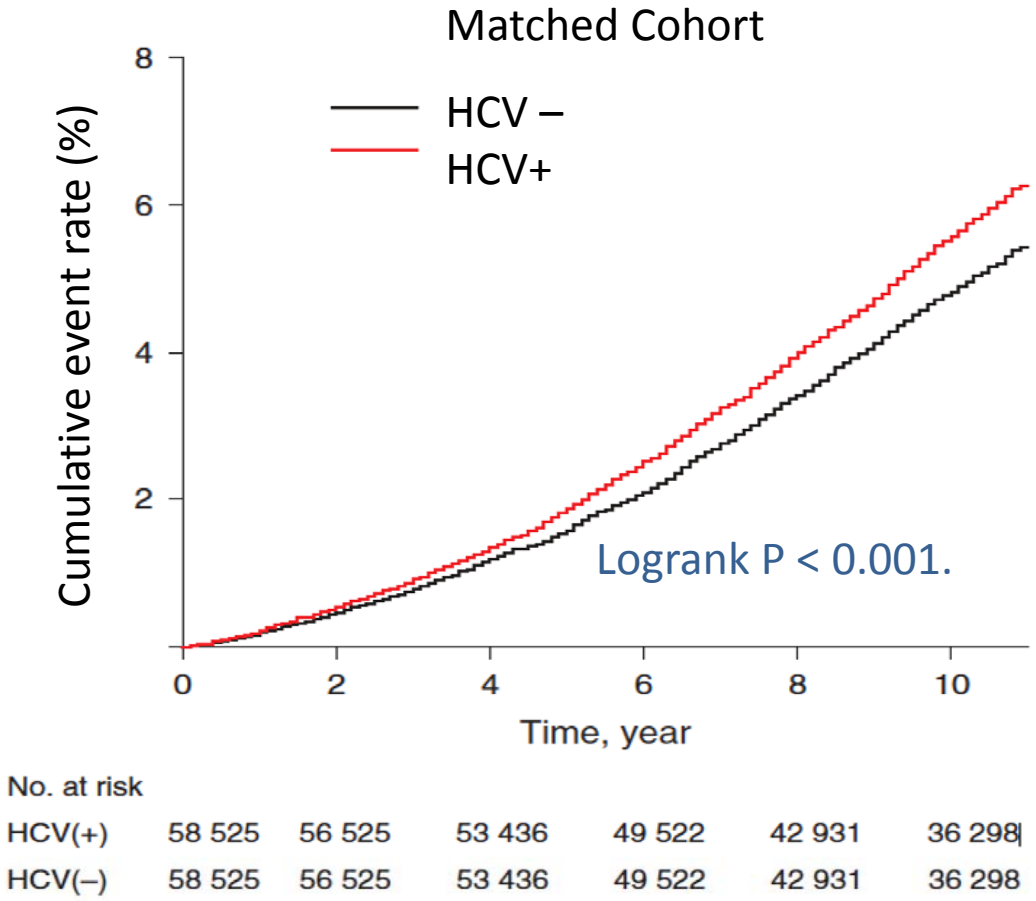

Neurological (e.g. cognitive impairment)
Pulmonary (e.g. idiopathic pulmonary fibrosis)
Cardiovascular (e.g. CAD, stroke)
Renal (e.g. glomerulo-nephritis)
Metabolic (e.g. diabetes)
Lymphoproliferative (e.g. B-cell malignancies)
Autoimmune (e.g. mixed cryoglobulinemia)
Dermatological (e.g. porphyria cutanea tarda)

Prevalence of extrahepatic manifestations in HCV

Extrahepatic manifestation		Estimated prevalence
Autoimmune	Mixed cryoglobulinaemia (MC)	19–54%
	Sjögren's syndrome	6–26%
	Thyroid disorders	10–25%
	Arthritis	<5%
Neurological	Peripheral neuropathy	9%
	Fatigue	35–54%
Dermatological	Most frequent: porphyria cutanea tarda, lichen planus, pruritus	15–20%
Cardiovascular	Vasculitis	4–40%
Cardiovascular/renal	Polyarteritis nodosa	8%
Metabolic	Diabetes mellitus	21%
Lymphoproliferative	B-cell malignancies (e.g. non-Hodgkin's lymphoma)	11% of MC
Renal	Membranoproliferative glomerulonephritis	10–60%

Monaco S, et al. *Clin Dev Immunol* 2012; Himoto T and Masaki T. *Clin Dev Immunol* 2012
Carvalho-Filho RJ, et al. *World J Gastroenterol* 2012;18:188–191; Ramos-Casals M, et al. *J Rheumatol* 2009;36:1442–1448
Ali A, Zein NN. *Cleve Clin J Med*. 2005;72:1005–1019; Ramos-Casals M, et al. *Rheumatology* 2003;42:818–828

Kaplan–Meier curves of cumulative event rate of dementia in the groups with and without HCV infection from matched 11-year HCV cohorts

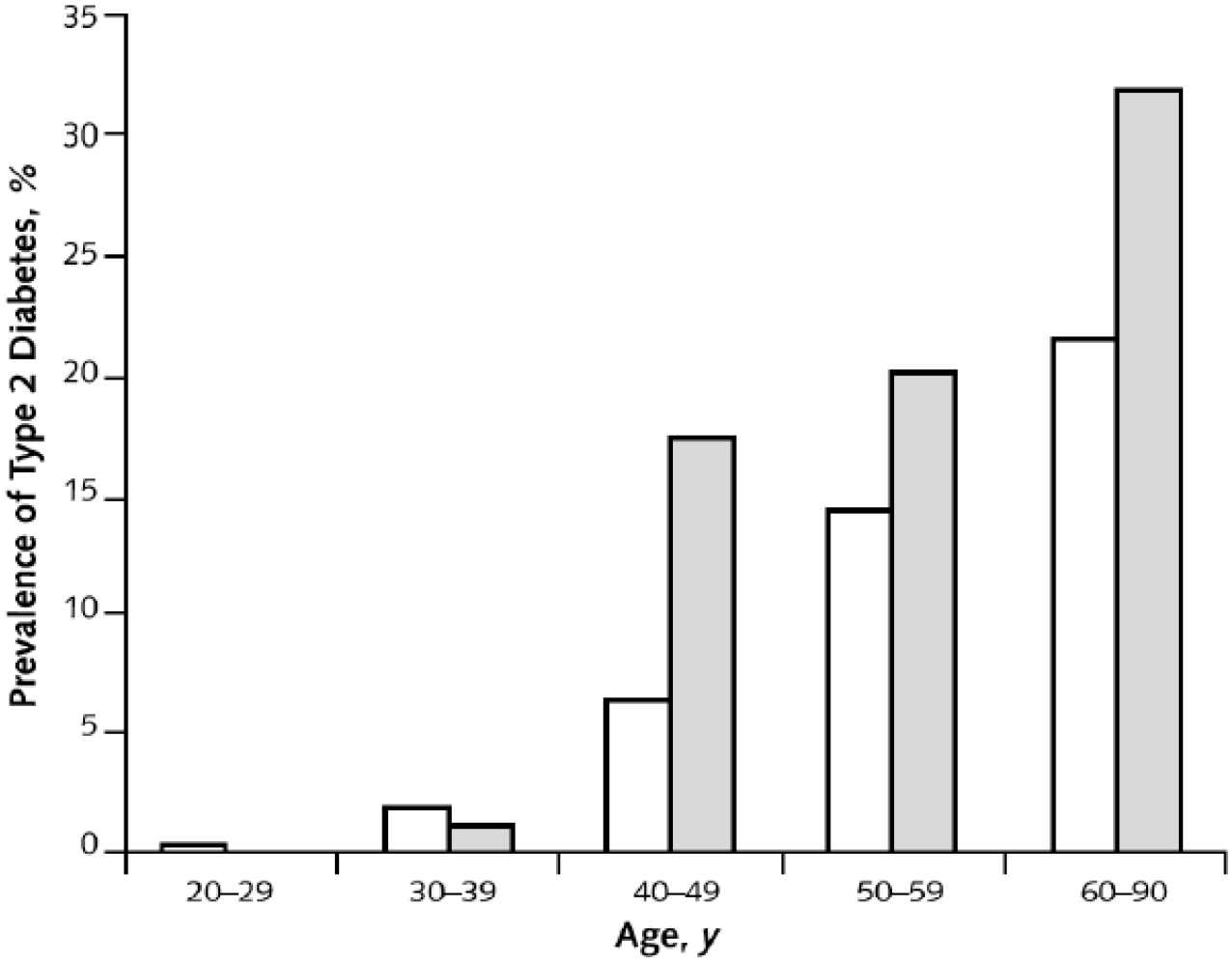


58.570 pairs matched with a 1:1 ratio by: sex, age, income, urbanization, diabetes, Hypertension, hypercholesterolemia, chronic obstructive pulmonary disease and depressive disorder.

(Chiu et al. European J Neurology in press)

Prevalence of type 2 diabetes in HCV+ *vs.* HCV- according to different classes of age

(The Third NHANES Survey, 1988-1994)



MEHTA et al, *Ann Intern Med* 2000;133:592-599

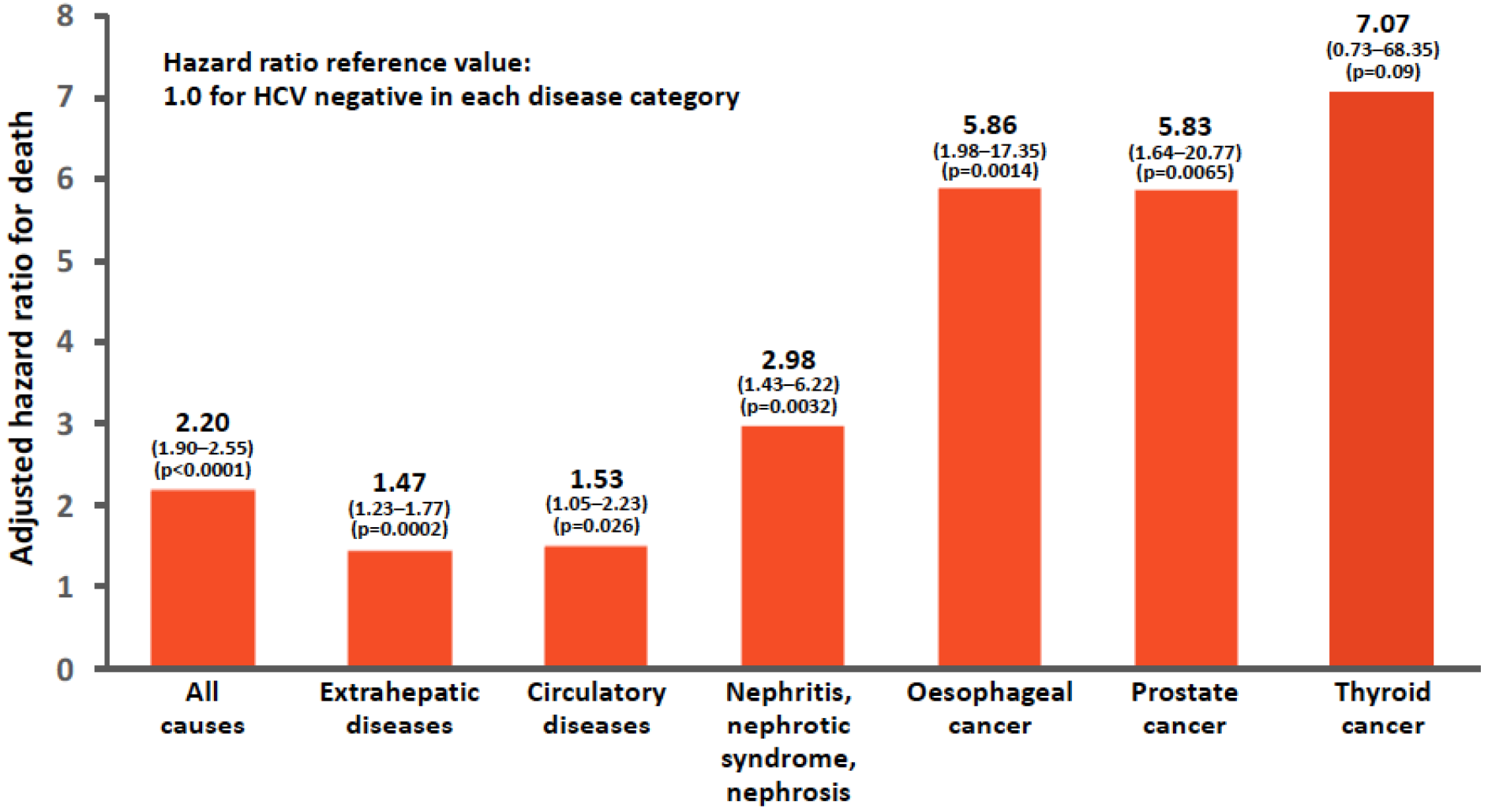
HCV patients without T2D have higher IR than controls

	HCV (n=121)	Controls (n=137)	*P*
Age	37.9 ± 8.9	41.8 ± 12.7	NS
Males	74 (61%)	74 (54%)	NS
BMI	26.5 ± 4.7	26.2 ± 4.6	NS
Waist-to-hip ratio	0.89 ± 0.08	0.88 ± 0.1	NS
C-peptide	826 ± 421	557 ± 298	<.001
HOMA-IR	2.4 ± 1.3	1.9 ± 1.2	.002

HUI et al, *Gastroenterology* 2003;125:1695-1704

Is HCV more than a liver disease?
Increased mortality 'beyond' the liver

The REVEAL HCV Cohort Study

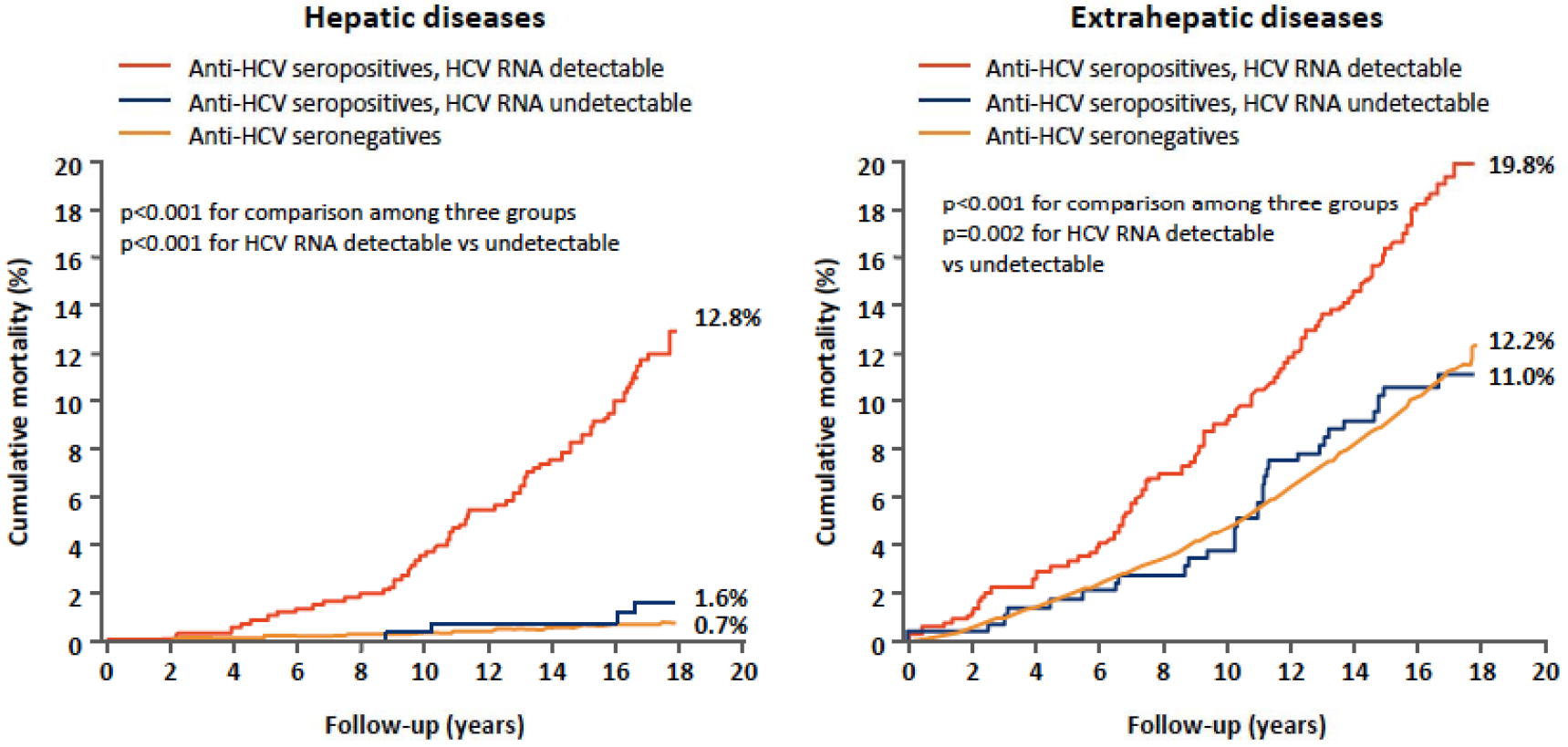


Lee et Al. J Infect Dis 2012; 206: 469-477

Chronic HCV increases mortality from hepatic and non-hepatic diseases

The REVEAL HCV Cohort Study

- 23 820 adults in Taiwan prospectively followed since 1991/2
- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA



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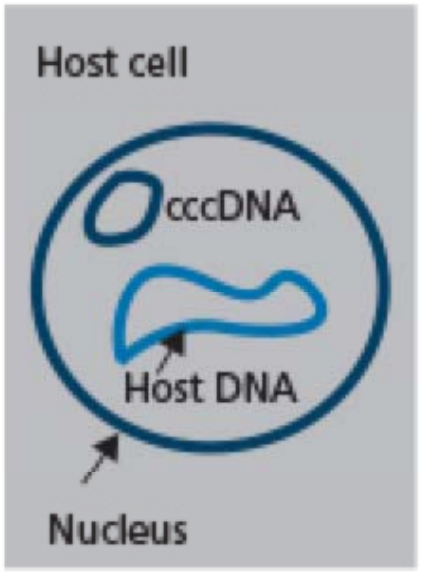
Differentiating Viral Strategies on a DNA or RNA Level

HCV

Definitve viral clearance
↓
SVR possible for HCV

HBV



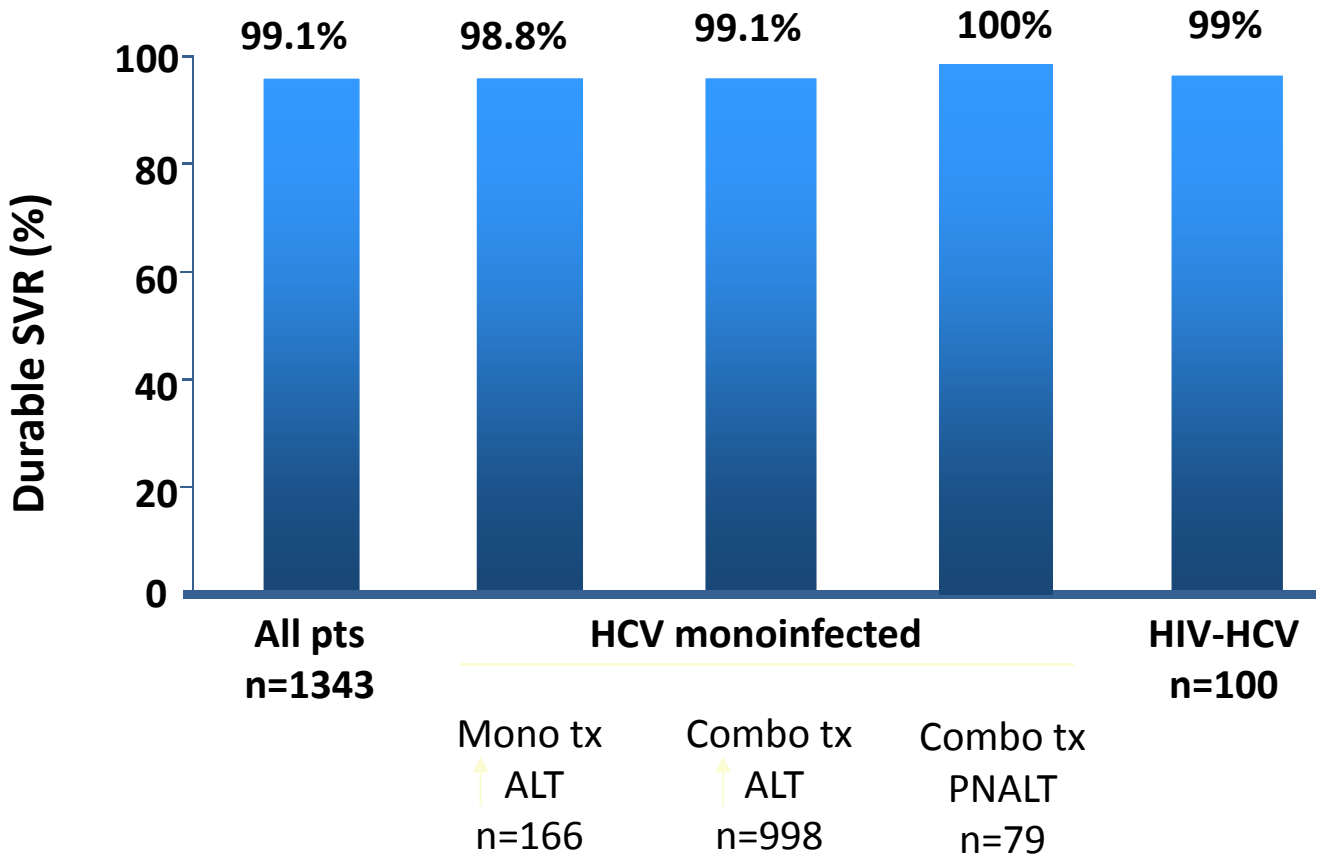
Long-term reduction of viral replication to lowest possible level

HIV

Lifelong suppression of viral replication

A SVR is Durable in Patients with HCV Infection Treated with PegIFNalfa2a and Ribavirin

Patients outcomes 4 years after therapy



Swain MG et al. Gastroenterology 2010

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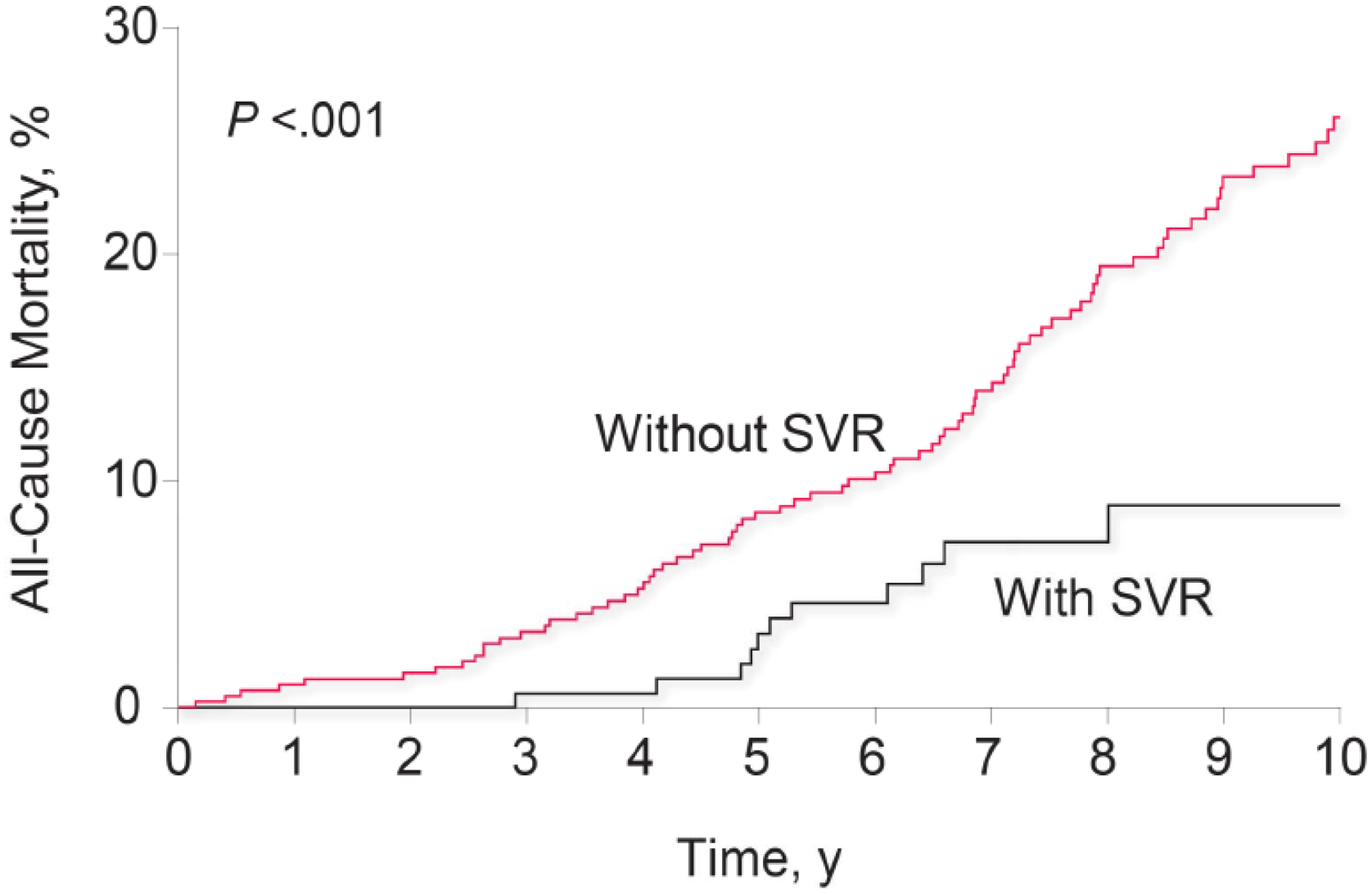
Mortality ratio of 2889 patients with chronic hepatitis C Followed for 65 months (1986-1998)

	Overall deaths		Liver-related deaths		Liver-unrelated deaths	
Patients	No.	SMR	No.	SMR	No.	SMR
Untreated	30	1.9 (1.3-28)	23	13.5 (8.6-20.3)	7	0.5 (0.2-1.0)
Interferon treated						
All	56	0.9 (0.7-1.1)	35	4.7 (3.3-6.5)	21	0.4 (0.2-0.6)
SVR	**7**	**0.4 (0.1-0.7)**	**2**	**0.8 (0.1-3.0)**	**5**	**0.3 (0.1-0.7)**
Non SVR	49	1.1 (0.8-1.5)	33	6.5 (4.5-9.1)	16	0.4 (0.2-0.7)

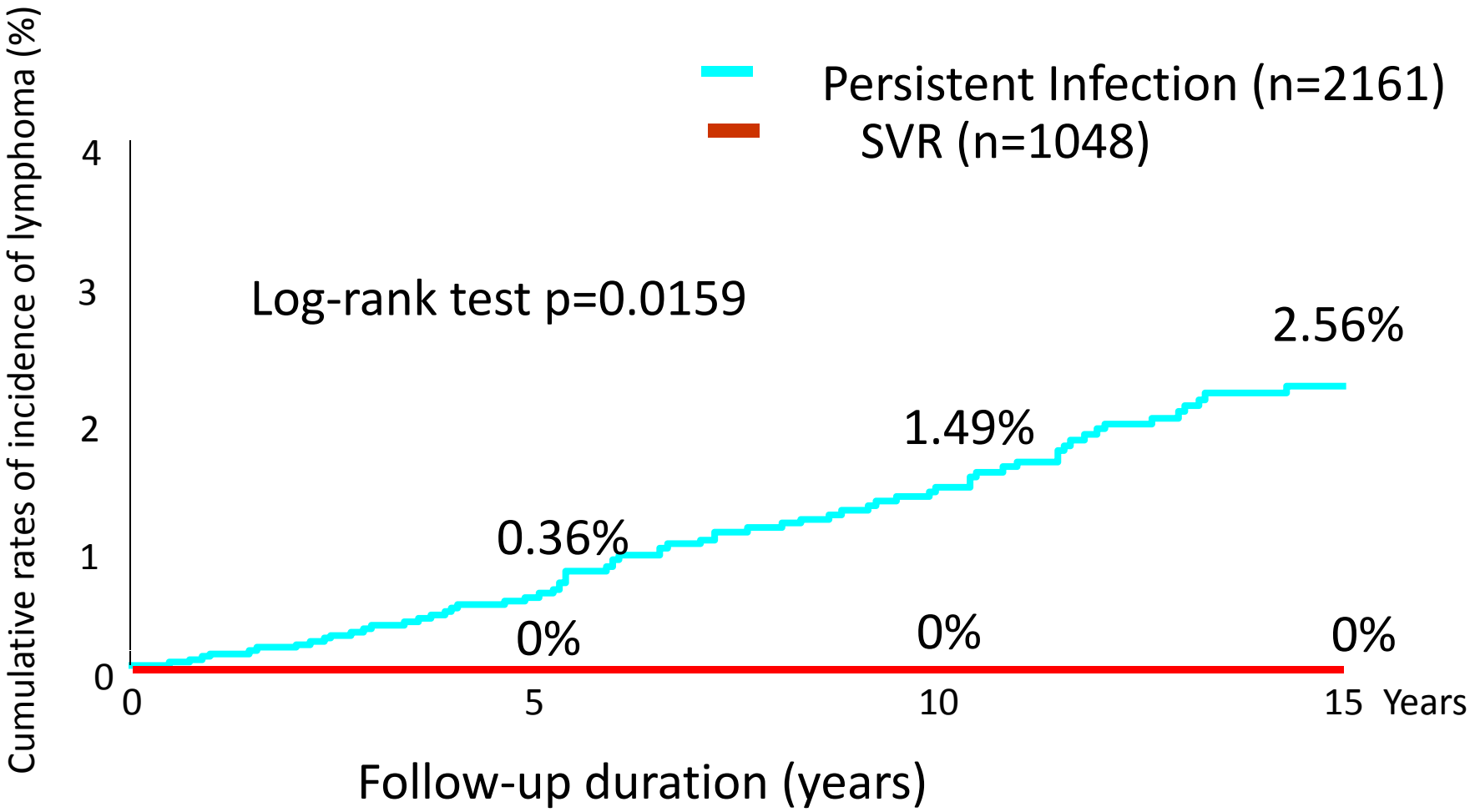
Yoshida et al Gastroenterology 2002;133:483-491

SVR is associated with a reduction in all-cause mortality



Van Der Meer et Al, JAMA 2012; 308: 2584-93

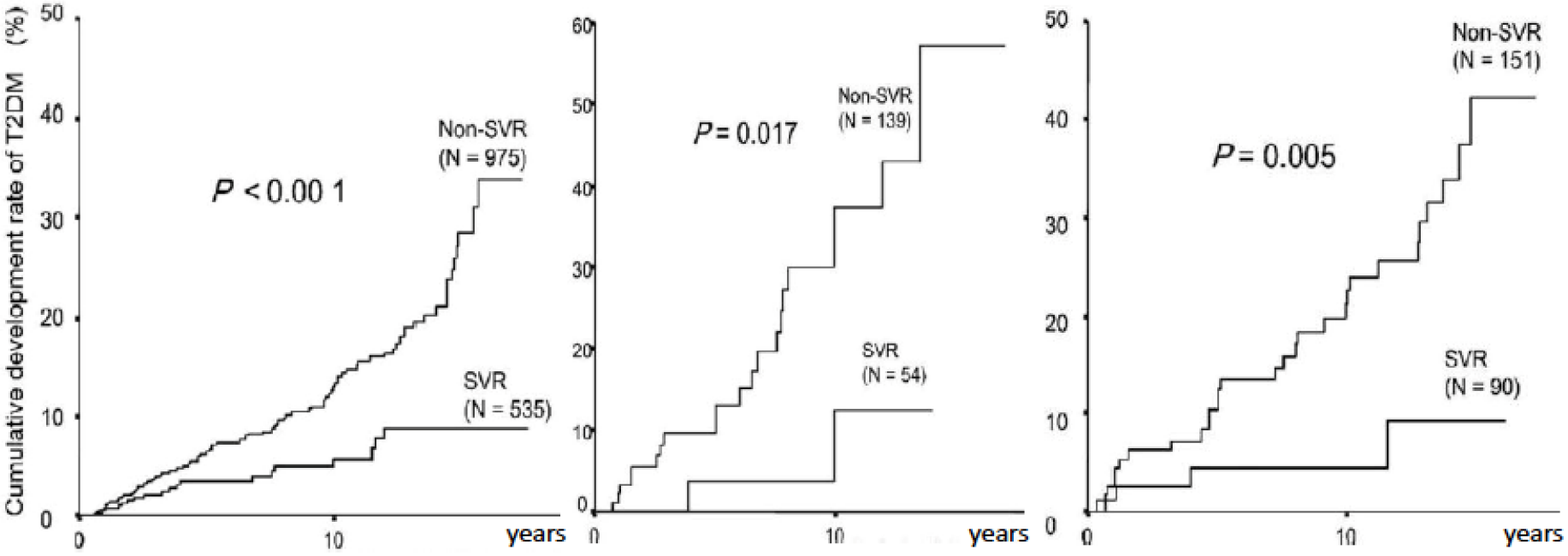
HCV Elimination Reduces The Incidence of Malignant Lymphoma



Kawamura Y, et al. Am J Med 2007;120:1034-1041

Cumulative incidence of type 2 diabetes in chronic hepatitis C: SVR *vs* non-SVR

Annual incidence of T2D in hepatitis C: 0.8-1.0%



Cure of HCV reduces the risk of developing T2D by more than two thirds

ARASE et al, *Hepatology* 2009;49:739-744

AP&T Alimentary Pharmacology and Therapeutics

Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan

C.-S. Hsu[*,†], J.-H. Kao[‡,§,¶,**], Y.-C. Chao[*,†], H. H. Lin[*,†], Y.-C. Fan[††], C.-J. Huang[†,††,‡‡] & P.-S. Tsai[§§,¶¶]

- 3,113 anti-HCV+ (208 treated)
- 12,452 uninfected controls from the Taiwan National Health Insurance Program Database
- HCV infection was associated with a 23% increase of the risk of stroke (after correction for risk factors)
- Antiviral treatment decreased this risk by ~60%

HSU et al, *Aliment Pharmacol Ther* 2013;38:415-23

The impact of SVR on histological outcome of HCV-induced cirrhosis

	Post-treatment				
Pre-treatment	F0	F1	F2	F3	F4
F0	1	2	0	0	0
F1	14	16	7	0	0
F2	7	23	12	2	4
F3	0	5	12	7	4
F4	0	1	2	6	5

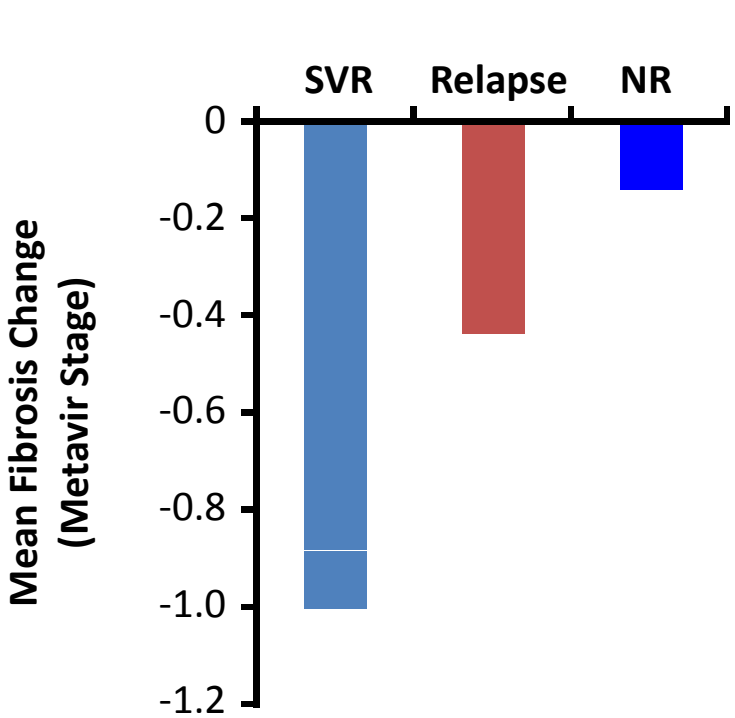
Post-treatment specimens were collected a median of 6 months after treatment cessation

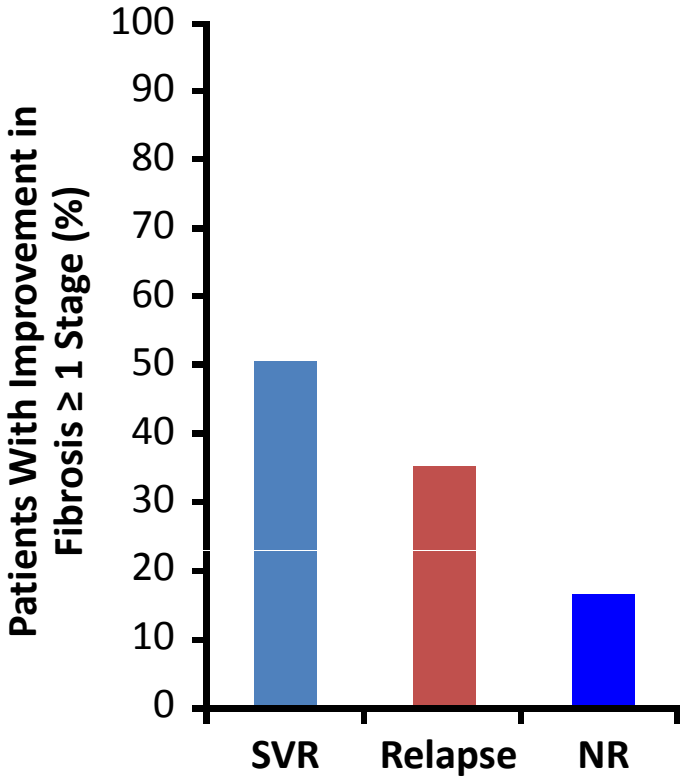
Comparison of liver fibrosis stage between pre-treatment and post-treatment paired liver biopsy in 126 patients

Maylin S et al Gastroenterology 2008

Improvement in Fibrosis at Week 72 Following Start of HCV Therapy

Varied With Response to Treatment





Everson GT, et al. Aliment Pharm Ther. 2008;27:542-551.

SVR AND PORTAL HYPERTENSION IN PATIENTS WITH COMPENSATED CIRRHOSIS

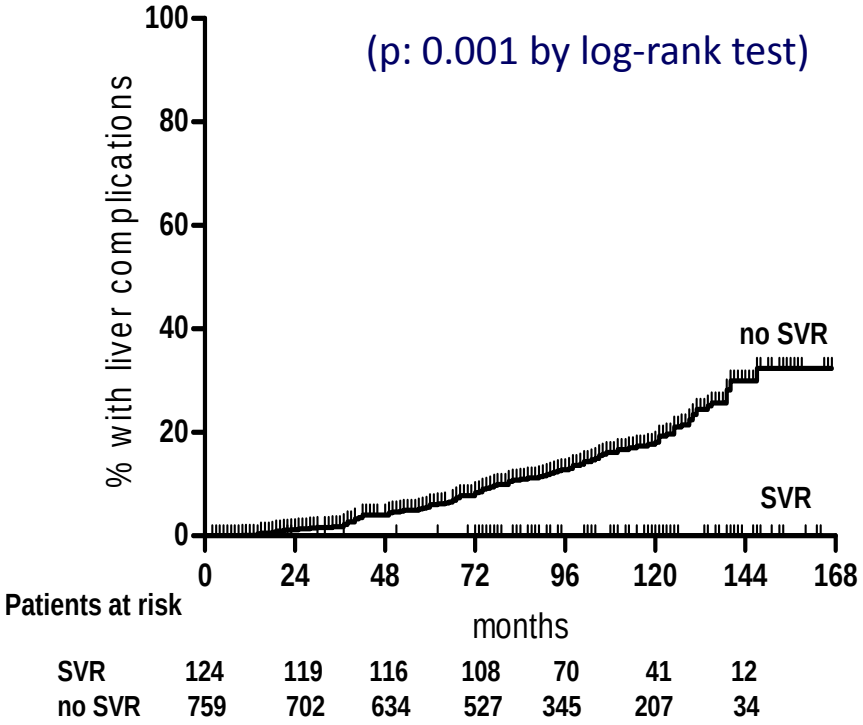
218 EV free cirrhotics **SVR 22.8 %**

Endoscopy every 3 ys **FU 11.4 ys**

	% developing esophageal varices
SVR	**0 %**
No SVR	**39.1 %**
Untreated	**31.8 %**

Bruno et al., Hepatology 2010

Impact of SVR on long-term outcome in 848 patients with HCV-related histologically-proven cirrhosis (stage 1) treated with IFN MT

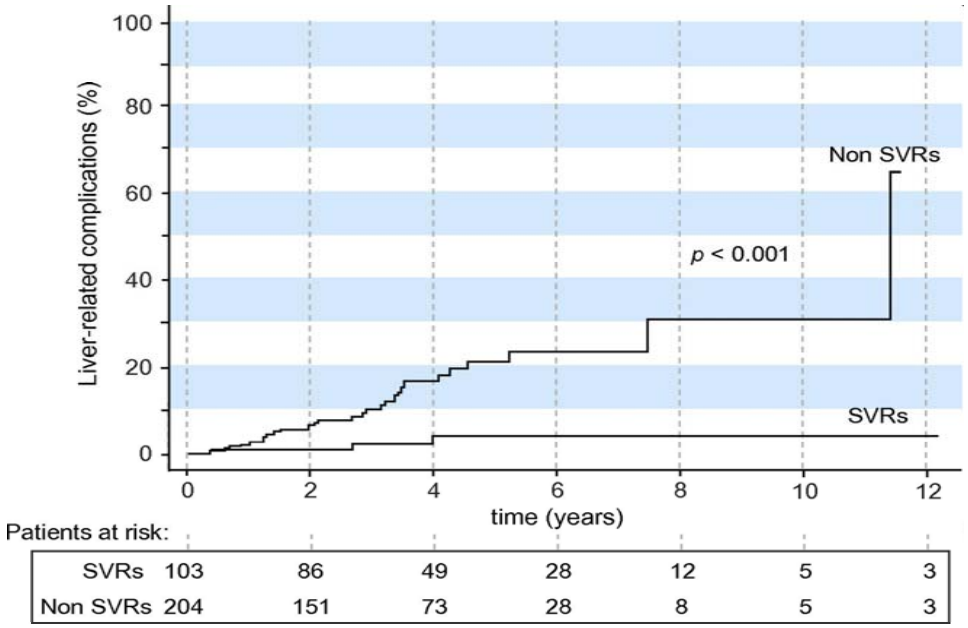


liver-related complications

Bruno S et al Hepatology 2007

CUMULATIVE INCIDENCE OF LIVER-RELATED COMPLICATIONS

307 cases with F3 or F4



Cardoso AC et al., J Hepatol 2010

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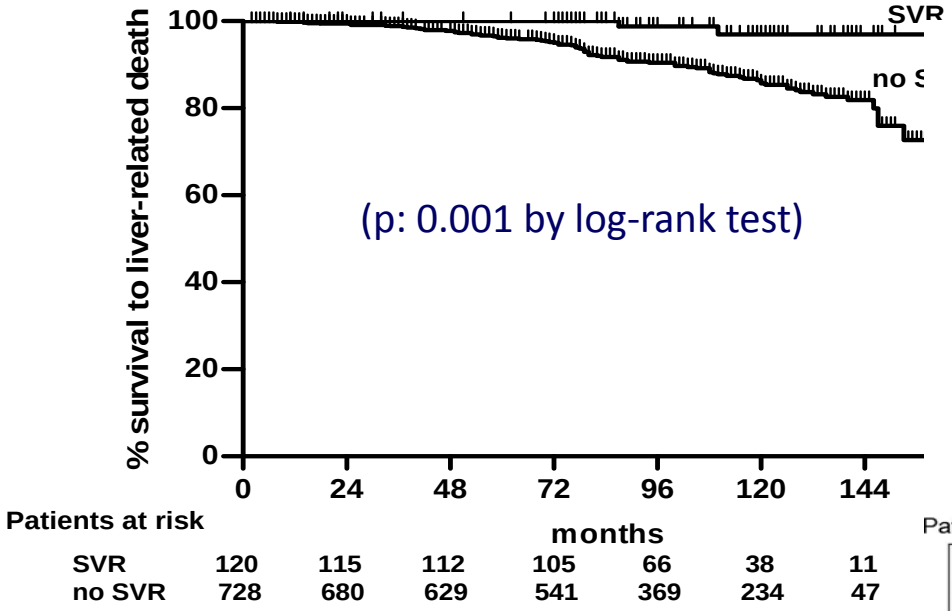
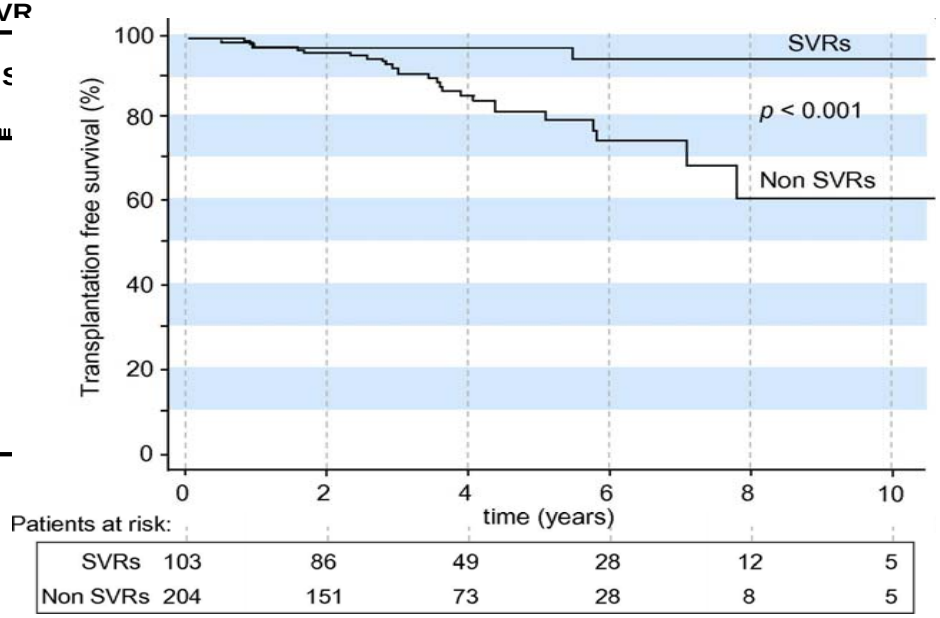


Liver mortality

Bruno S et al Hepatology 2007

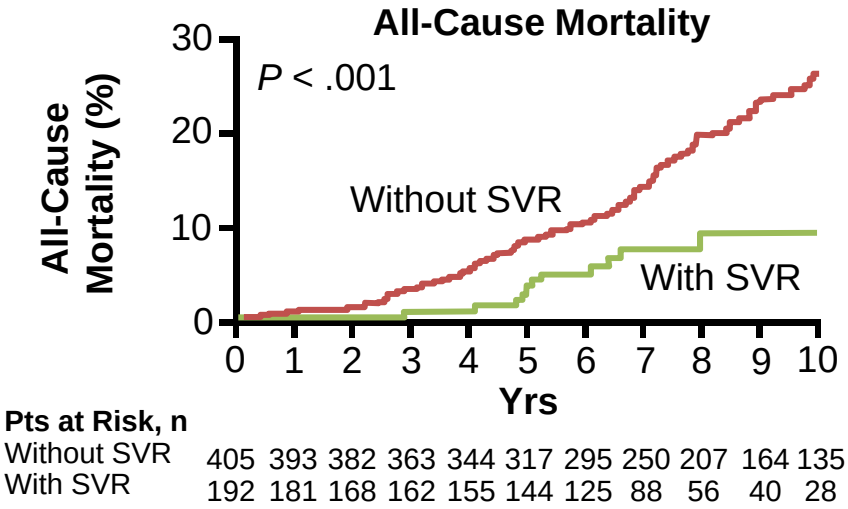
CUMULATIVE INCIDENCE OF LIVER-RELATED DEATH

307 cases with F3 or F4



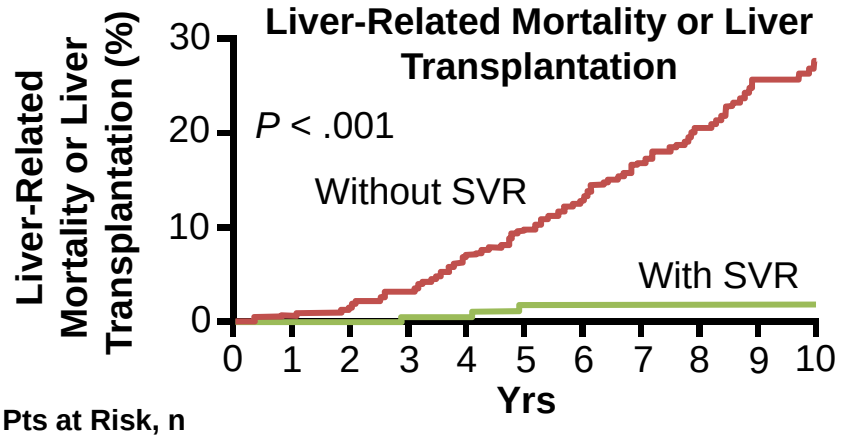
Cardoso AC et al., J Hepatol 2010

Survival Outcomes in Pts With CHC and Advanced Fibrosis With/Without SVR



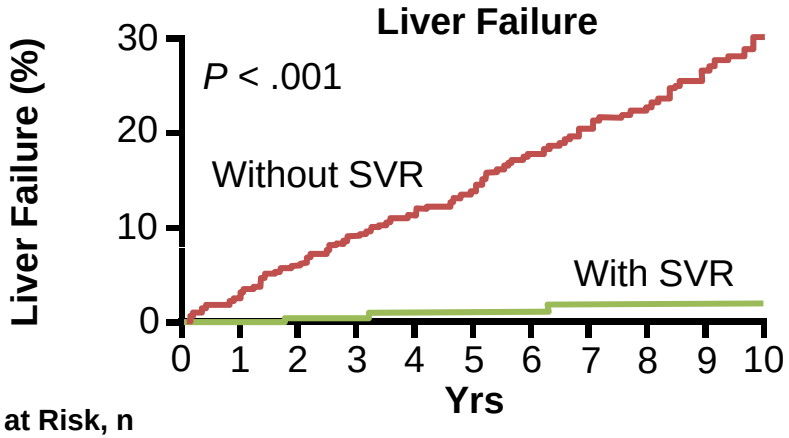
Pts at Risk, n

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



Pts at Risk, n

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

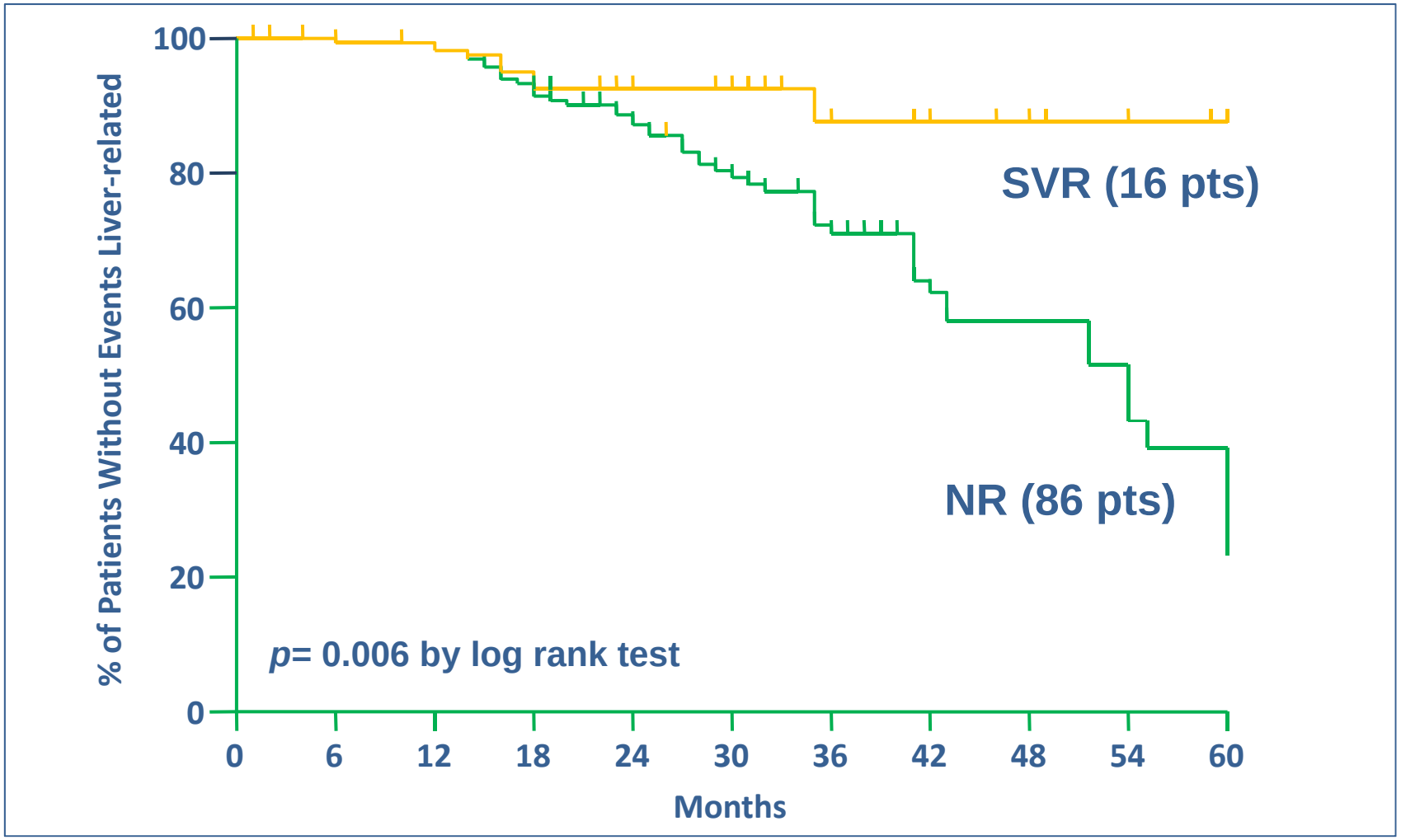


Pts at Risk, n

Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

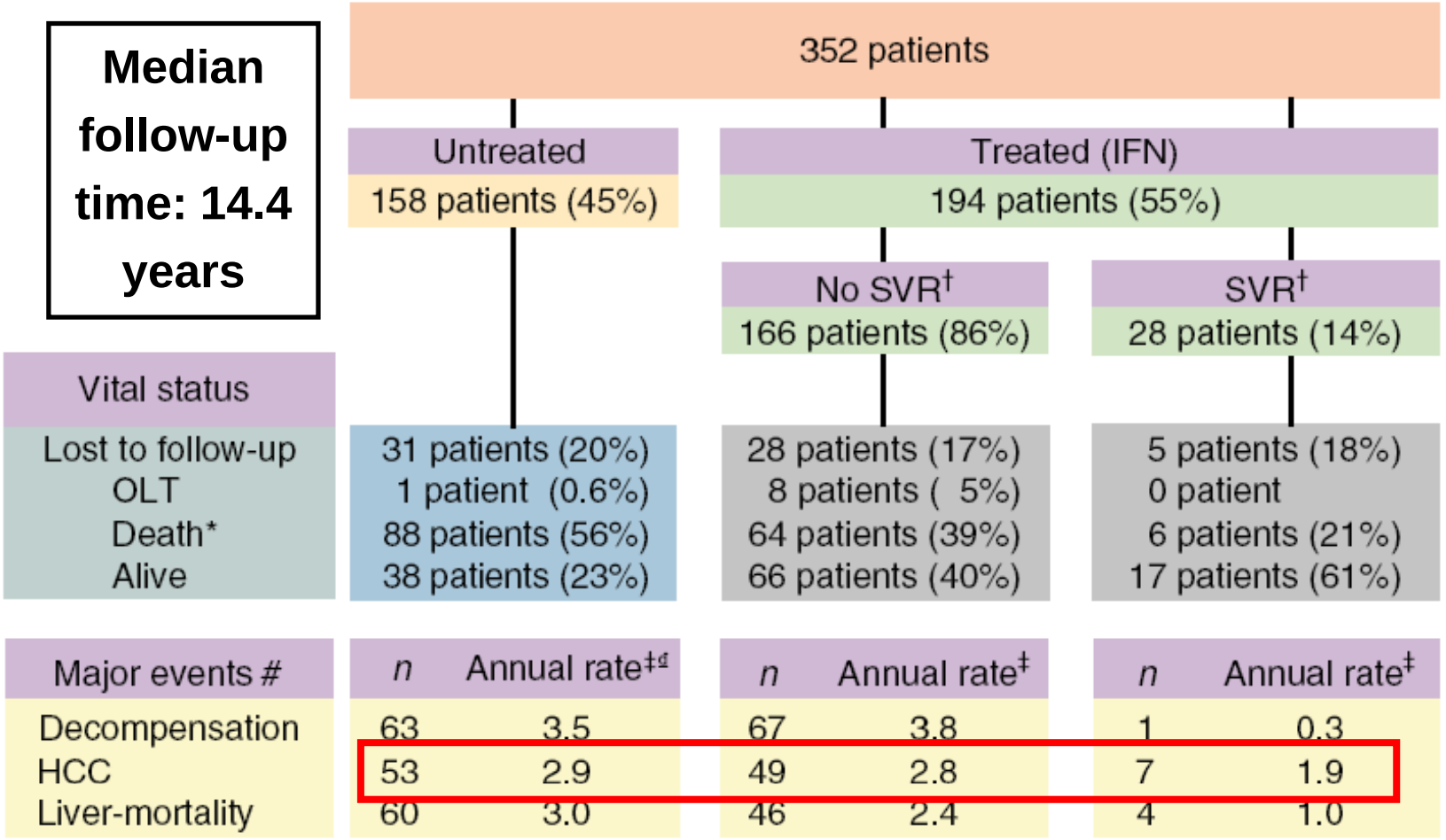
Van der Meer AJ, et al. JAMA. 2012;308:2584-2593.

Event-free survival according to response to therapy in 102 patients with HCV-induced cirrhosis and portal hypertension (stage 2)



Di Marco V et al J Hepatol 2007

Annual rate of HCC occurrence (% person-years) in patients with HCV-related cirrhosis according to IFN treatment

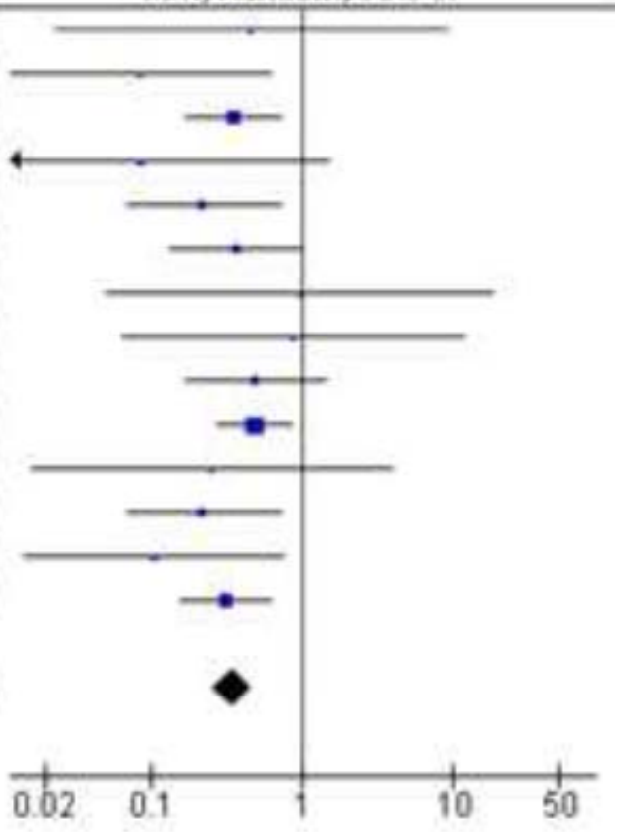


Bruno S et al Am J Gastroenterol 2009

HCC occurrence in patients with HCV-related cirrhosis according to SVR

Study or Subgroup	SVR Events	SVR Total	NSVR Events	NSVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Azzaroli 2004	0	21	2	50	1.0%	0.46 [0.02, 9.27]
Braks 2007	1	37	24	76	2.3%	0.09 [0.01, 0.61]
Bruno 2007 (1)	7	124	122	759	16.0%	0.35 [0.17, 0.73]
Floreani 2008 (2)	0	40	5	38	1.1%	0.09 [0.00, 1.51]
Hasegawa 2007 (3)	3	48	16	57	6.3%	0.22 [0.07, 0.72]
Hung 2006	5	73	11	59	8.7%	0.37 [0.14, 1.00]
Nishiguchi 1995	0	7	2	38	1.0%	0.97 [0.05, 18.43]
Okanoue 1999	0	2	7	38	1.3%	0.87 [0.06, 11.79]
Shioda 1999	4	204	18	448	7.6%	0.49 [0.17, 1.42]
Shiratori 2005	11	64	73	207	26.9%	0.49 [0.28, 0.86]
Tanaka 1998	0	8	10	47	1.2%	0.25 [0.02, 3.96]
Veldt 2008	3	142	32	337	6.4%	0.22 [0.07, 0.71]
Yoshida 1999 (4)	1	53	30	168	2.2%	0.11 [0.01, 0.76]
Yu 2006	9	85	27	80	18.3%	0.31 [0.16, 0.63]
Total (95% CI)		**908**		**2402**		**0.35 [0.26, 0.46]**

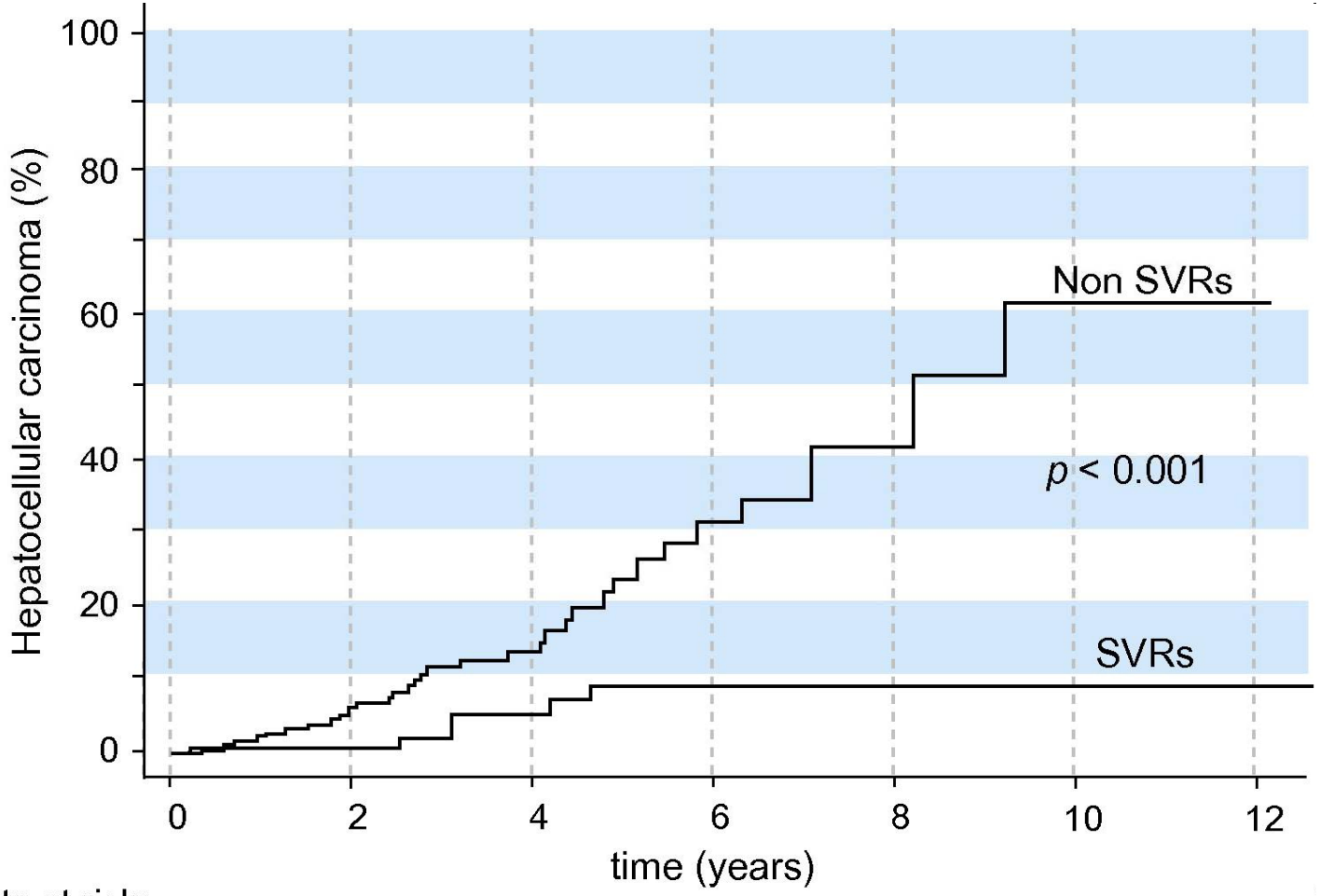
Heterogeneity: $Chi^2 = 8.67$, df = 13 (P = 0.80)
Test for overall effect: Z = 7.06 (P < 0.00001)



Singal AK Clin Gastroenterol Hepatol 2009

CUMULATIVE INCIDENCE OF HEPATOCELLULAR CARCINOMA

307 cases with F3 or F4



Patients at risk:

SVRs	103	86	49	28	12	5	3
Non SVRs	204	151	73	28	8	5	3

Cardoso AC et al., J Hepatol 2010

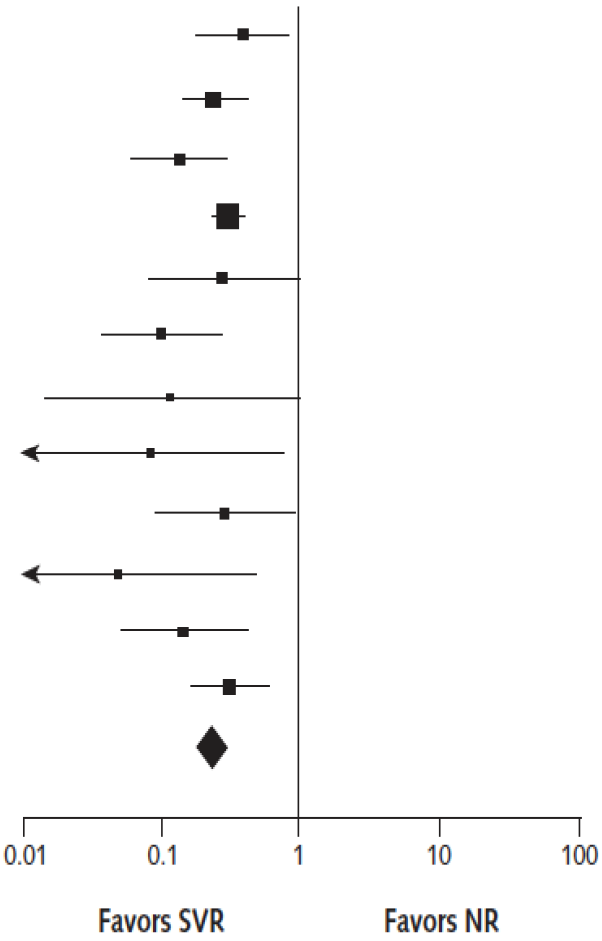
Association of SVR With the Development of HCC in HCV infection

Forest plot of adjusted hazard effects in persons at **all stages of fibrosis**

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Asahina et al, 2010 (36)	–0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	–1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	–1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	–1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	–1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	–2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	–2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	–2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	–1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	–3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	–1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	–1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



Morgan RL et al. Ann Intern Med 2013

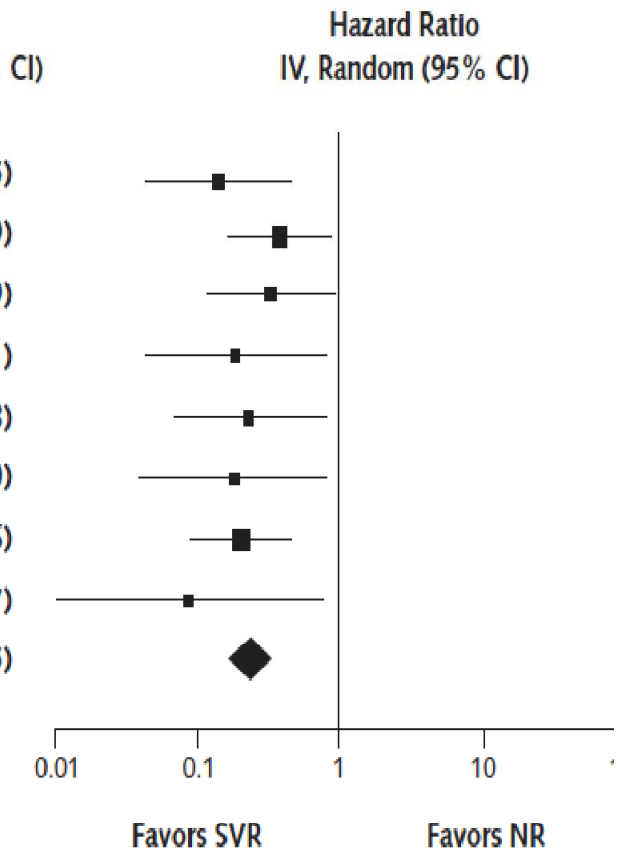
Association of SVR With the Development of HCC in HCV infection

Forest plot of adjusted hazard effects in Persons with **advanced liver disease**

Study, Year (Reference)	log(Hazard Ratio)	SE	Total		Weight, %	Hazard Ratio IV, Random (95% CI)
			SVR	NR		
Braks et al, 2007 (37)	–1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	–0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	–1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	–1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	–1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	–1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	–1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	–2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$



Morgan RL et al. Ann Intern Med 2013

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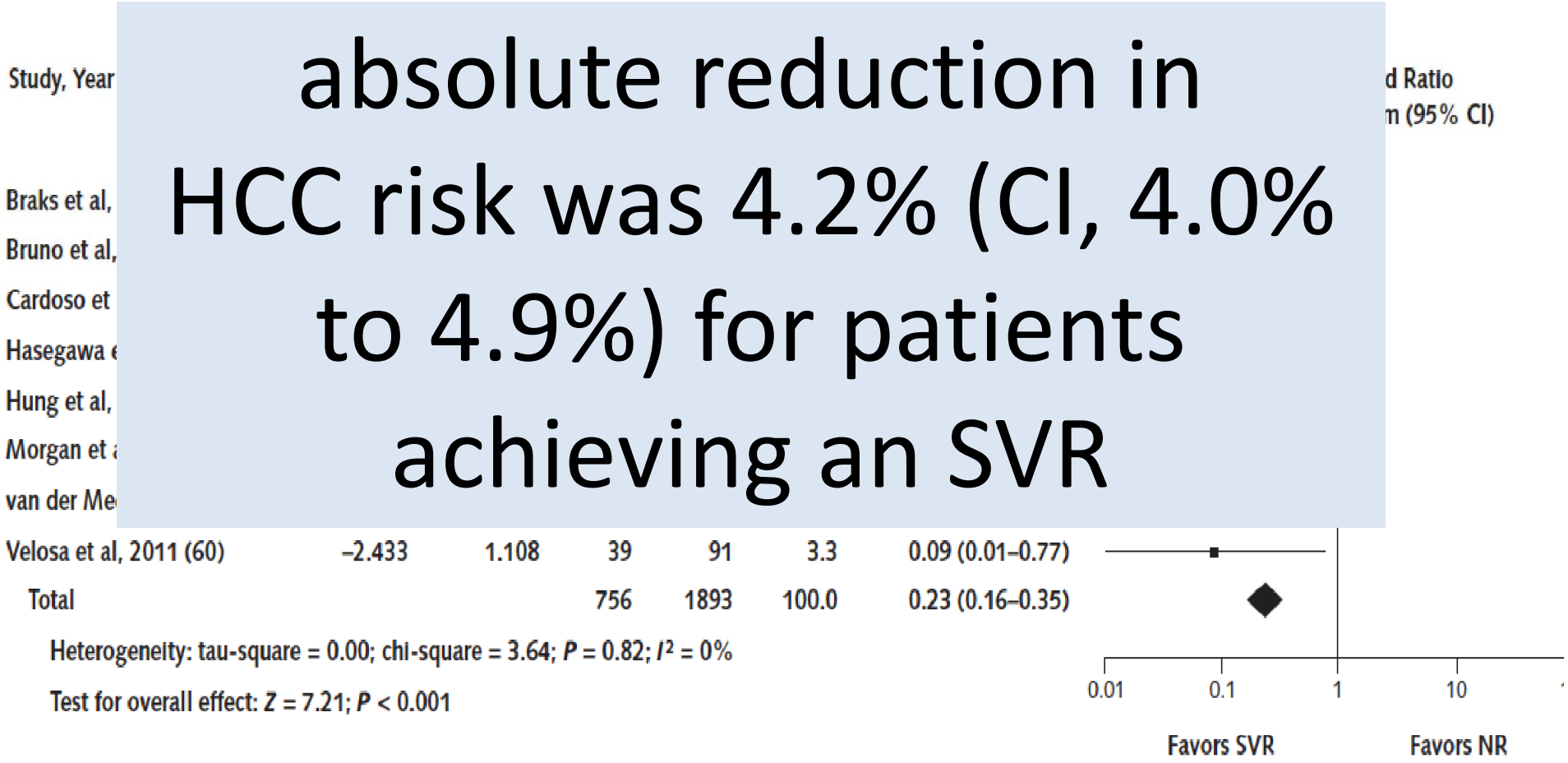
absolute reduction in HCC risk was 4.2% (CI, 4.0% to 4.9%) for patients achieving an SVR



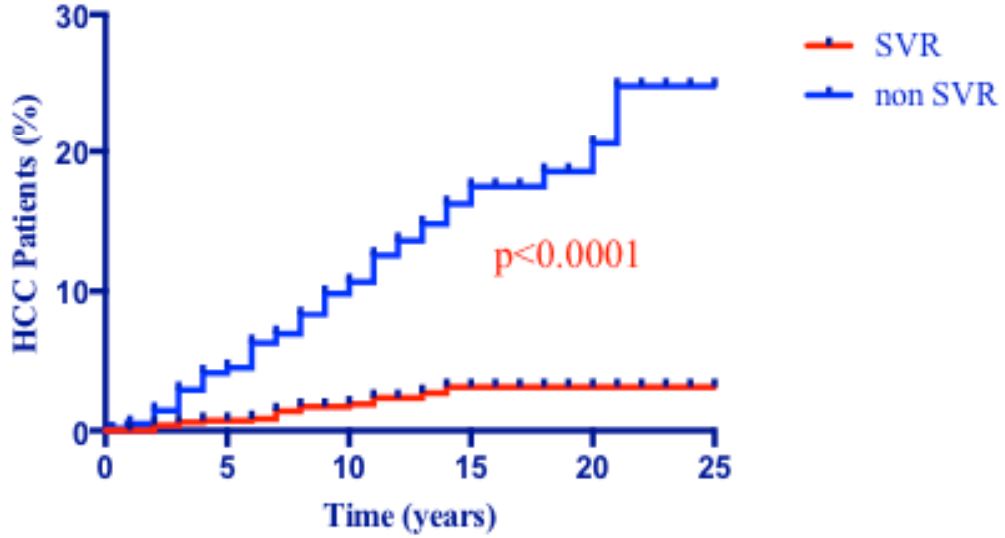
Morgan RL et al. Ann Intern Med 2013

HEPATOCELLULAR CARCINOMA (HCC) INCIDENCE IN CHRONIC HEPATITIS C PATIENTS (CHC) ACCORDING TO SUSTAINED VIROLOGIC RESPONSE (SVR)

HCC incidence – SVR /non-SVR

MEDICAL UNIVERSITY OF VIENNA

SVR group = 1.8% vs. Non-SVR = 12.1%, p<0.0001



T. Purevsambuu et al. EASL 2014; abstr Oral 125

1371 patients
Diagnosed 1989-2011
Treated

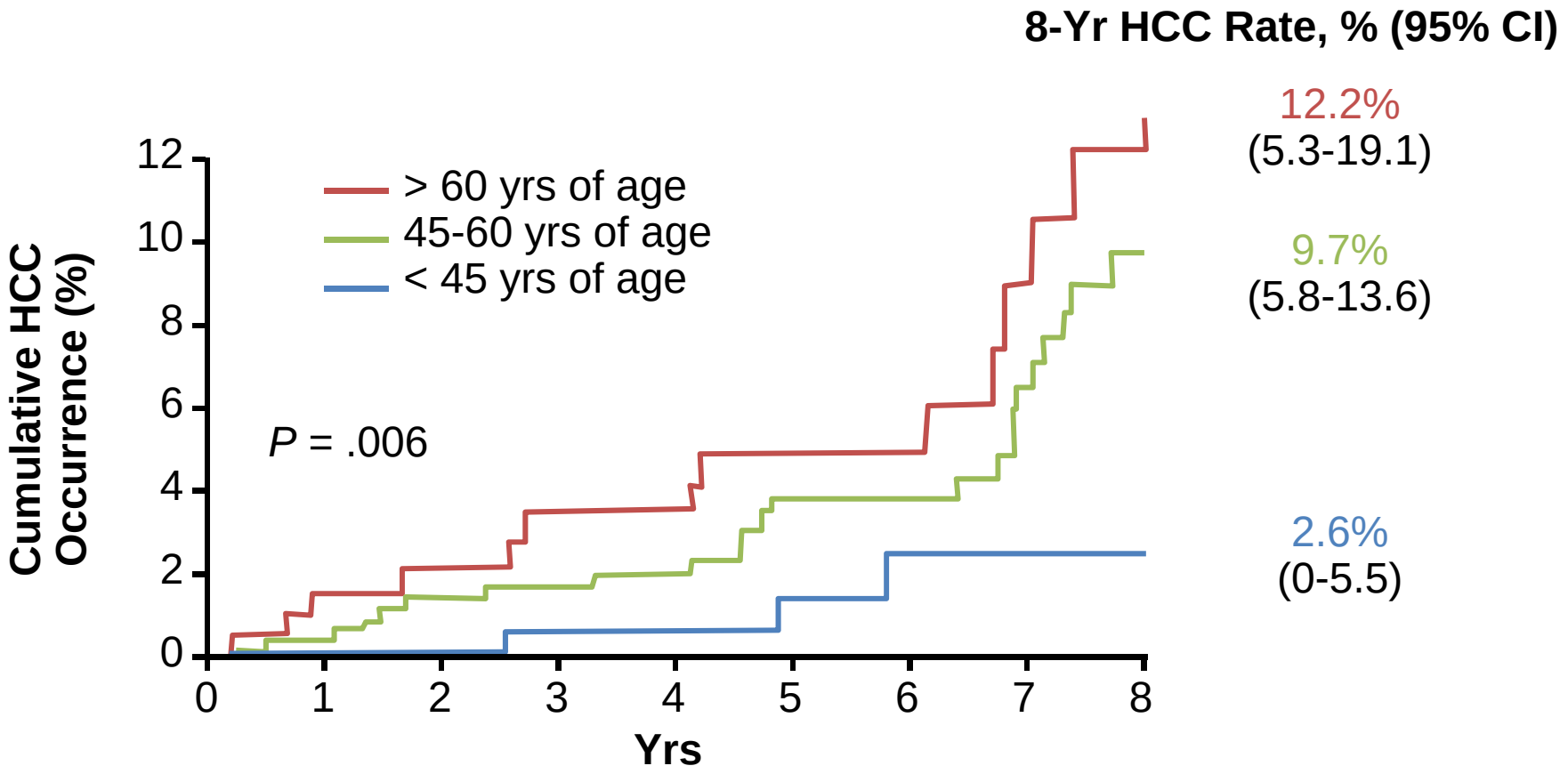
HCC-incidence
F4/SVR: 7.7%
F4/non-SVR 21.9%
(p = 0.003)

F3/SVR : 1.4%
non-SVR: 5.6%
(p = 0.04).

F0–2/SVR 0.2%
Non-SVR 2.9%
(p = 0.01).

Age as a Risk Factor for HCC Following SVR in HCV Pts With Advanced Fibrosis

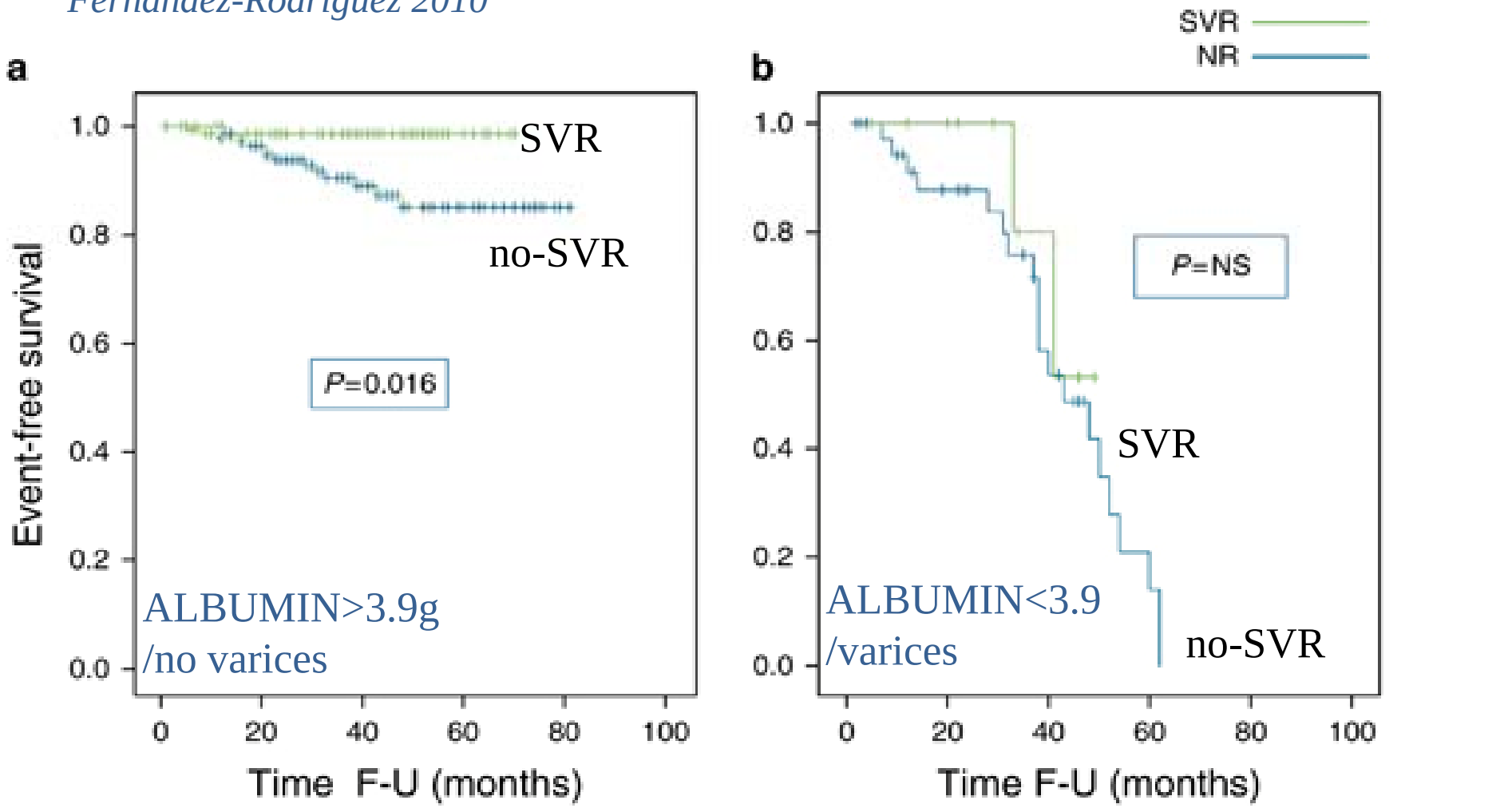
- HCC risk increased with age; highest for those > 60 yrs



Van der Meer AJ, et al. AASLD 2013. Abstract 143. Reproduced with permission.

LIVER EVENT-FREE SURVIVAL ACCORDING TO STAGE OF CIRRHOSIS AT THE TIME OF ANTIVIRAL THERAPY

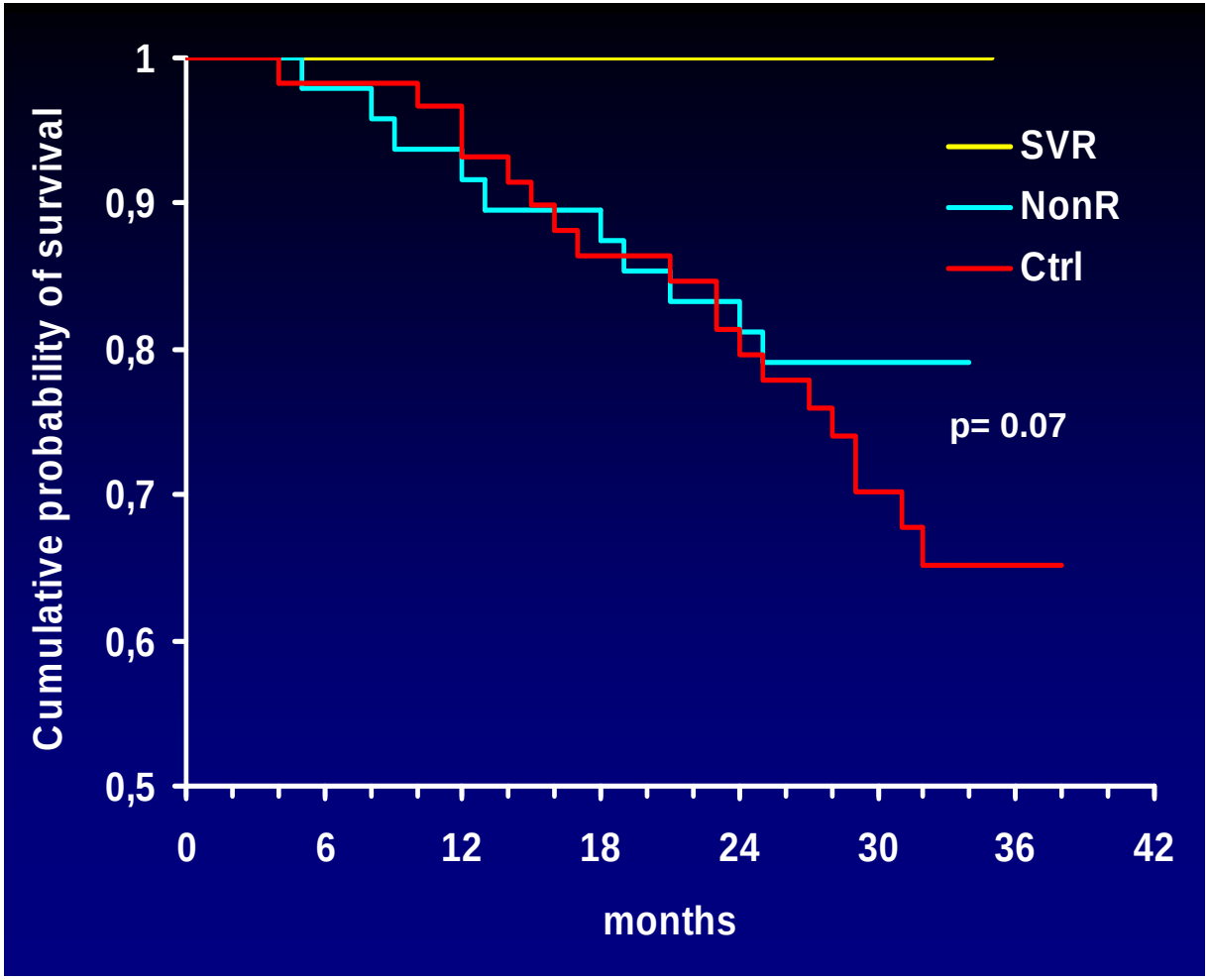
Fernandez-Rodriguez 2010



Subjects at risk

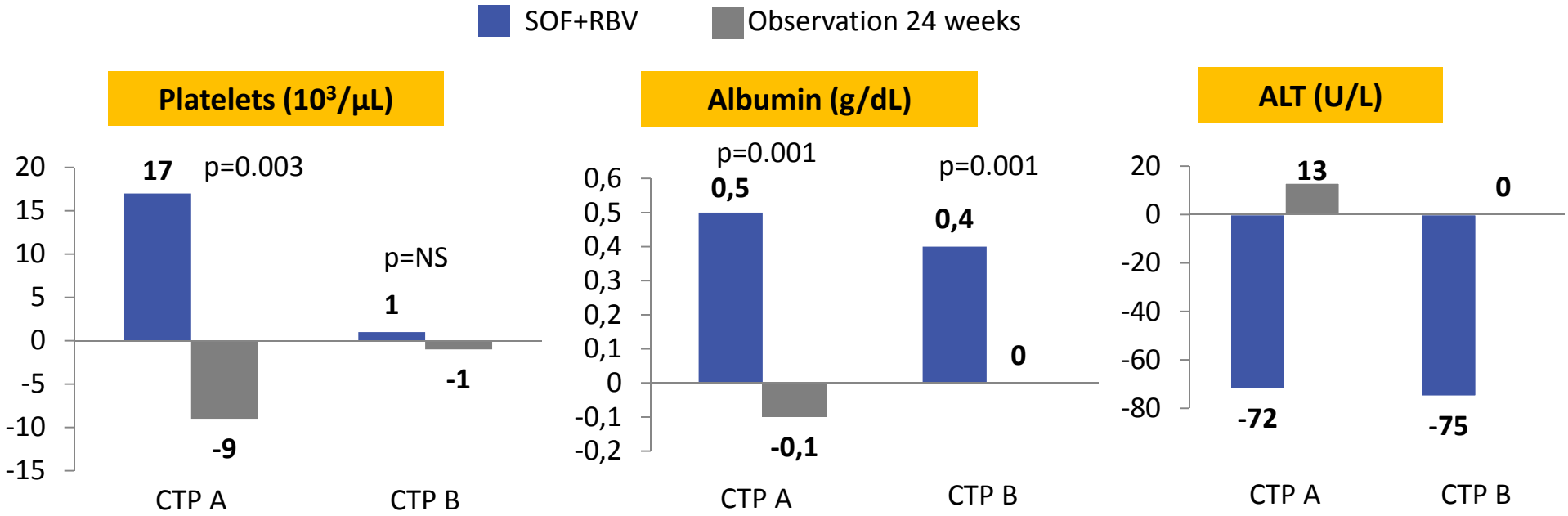
										Cumulative events 8A	Cumulative events 8B
NR	146	127	107	87	67	36	25	12	2	14	20
SVR	73	54	34	14	0	9	7	2	0	1	2

Cumulative probability of survival of SVRs versus Non SVRs and controls in patients with **Decompensated HCV cirrhosis**



Iacobellis A et al J Hepatol 2007

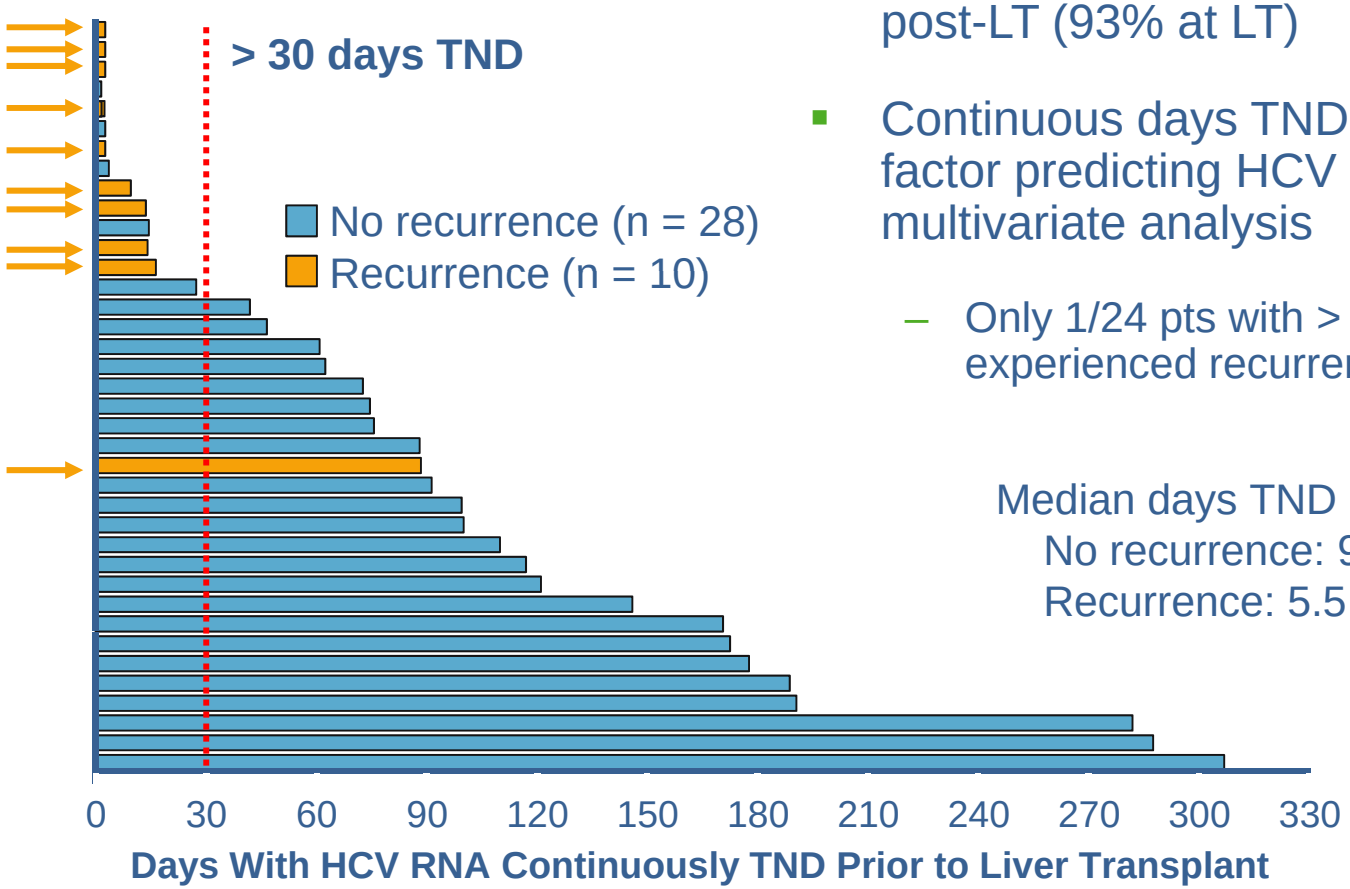
Laboratory and Clinical Event Changes



	Ascites		Hepatic Encephalopathy	
Patients, n	**SOF + RBV n=25**	**Observation n=25**	**SOF + RBV n=25**	**Observation n=25**
Baseline	6	9	5	2
Week 12	5	8	3	3
Week 24	0	7	0	4

Afdhal N, EASL, 2014, O68

Duration of Undetectable HCV RNA Before Transplant Predicted Lack of Recurrence



- 64% of pts HCV RNA negative 12 wks post-LT (93% at LT)
- Continuous days TND pre-LT only factor predicting HCV recurrence in multivariate analysis
  - Only 1/24 pts with > 30 days TND experienced recurrence

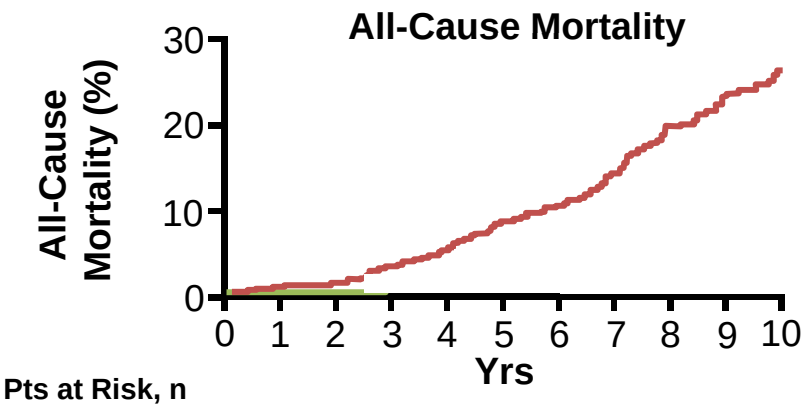
Median days TND (*P* < .001)
No recurrence: 95
Recurrence: 5.5

Curry MP, et al. AASLD 2013. Abstract 213. Reproduced with permission.

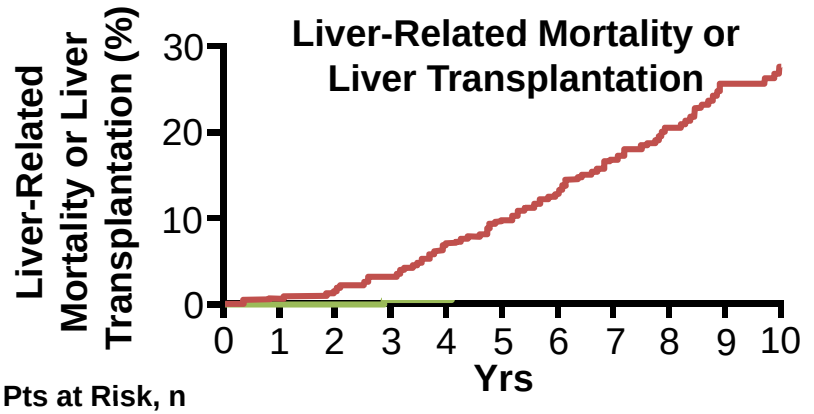
Conclusions

- HCV multiorgan, curable disease
- Natural history multifaceted
- Antiviral treatment potentially capable of reverting hepatic and extra-hepatic damage
- HCC surveillance in advanced fibrosis

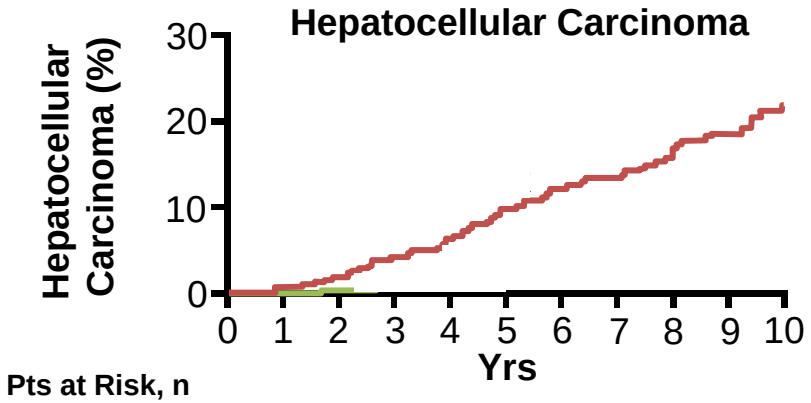
Survival Outcomes in Pts With CHC and Advanced Fibrosis With/Without SVR



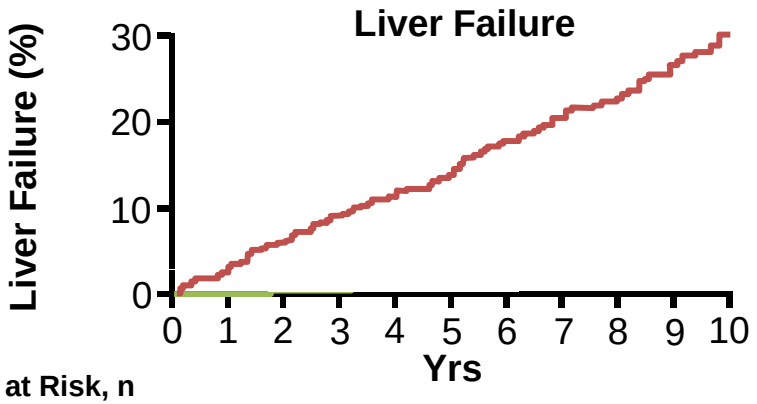
Pts at Risk, n											
Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28



Pts at Risk, n											
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



Pts at Risk, n											
Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27



Pts at Risk, n											
Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

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