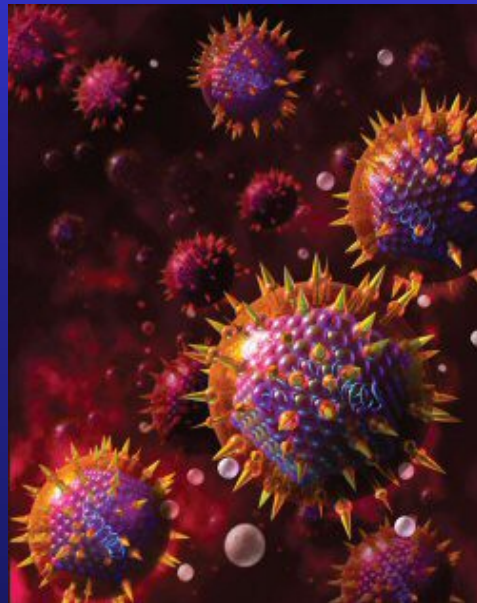
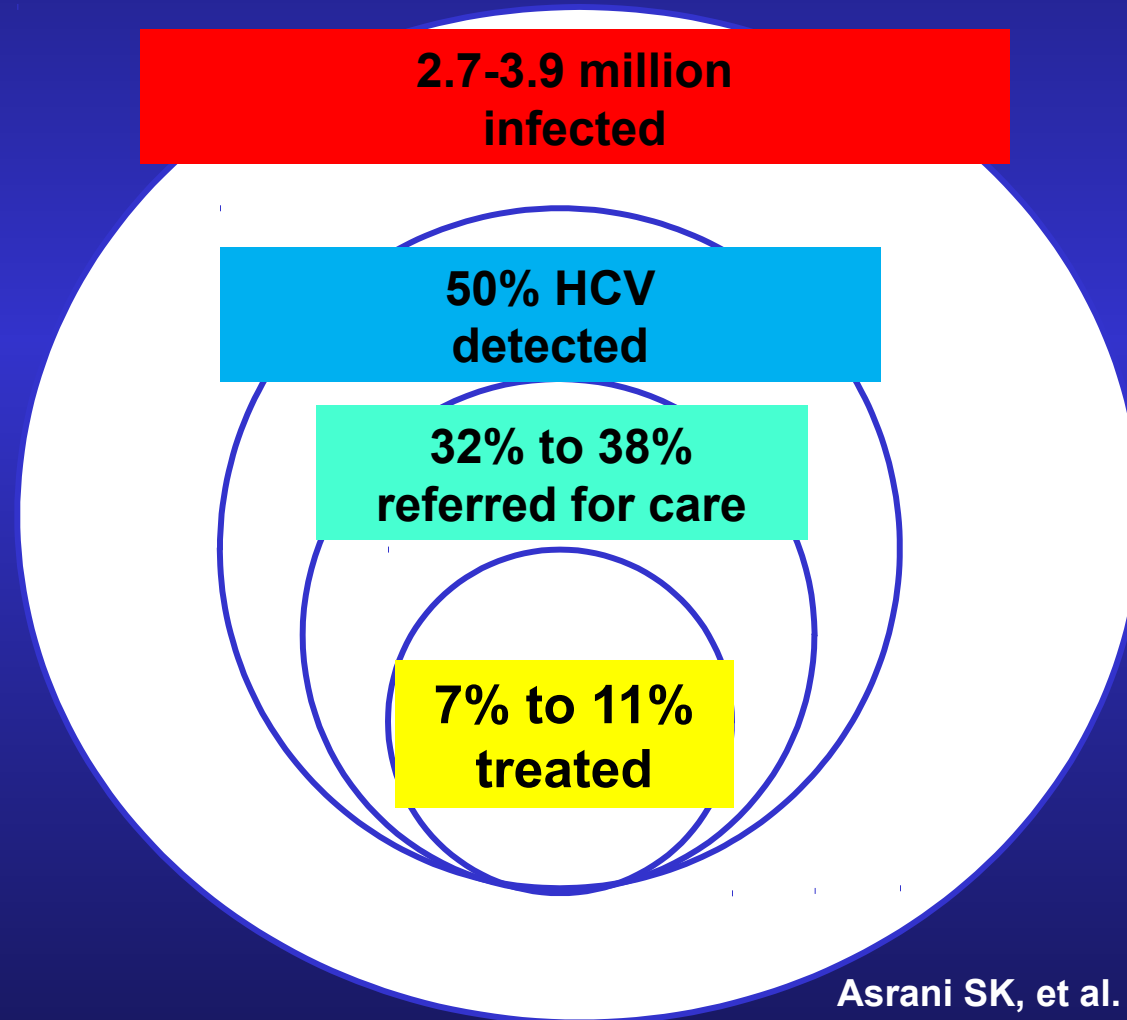


The long term impact of treatment on the outcome of Hepatitis C

Prof.Nurdan Tözün
Acıbadem University
Turkey



Currently, Very Few HCV Patients Are Treated



Natural history of hepatitis C from retrospective, prospective and retrospective-prospective cohort studies (A)

Retrospective studies

Intervals from exposure	9-29 years
Cirrhosis	17-55% (mean 42%)
HCC	1-23%
Liver deaths	4-15%

Prospective studies

Intervals from exposure	8-16 years
Cirrhosis	7-16% (mean 11%)
HCC	0.7-1.3%
Liver deaths	1.3-3.7%

Natural history of hepatitis C from retrospective, prospective and retrospective-prospective cohort studies (B)

Retrospective -Prospective Cohort Studies

- Children and young men or women

Exposure interval	9-45 years
Cirrhosis	0.3-5.9% (mean 2.1%)
HCC	0
Liver deaths	0-2.1%

- Middle-aged people with post-transfusion hepatitis

Exposure interval	23 years
Cirrhosis	15%
HCC	1.9%
Liver deaths	2.8%

EXPECTATIONS FROM HCV TREATMENT WITH ANTIVIRALS

- **Reduce the risk of :**
 - **Developing HCC**
 - **Liver decompensation / complications of LC**
 - **Liver related death**
 - **Overall death in HCV cirrhosis**
- **Improve quality of life**
- **Decrease the disease burden in the community**
- **Control the economic burden associated with advanced disease**

**To which extent these
expectations are fulfilled with
antiviral therapies ?**

Effects of a Sustained Virologic Response on Outcomes of Patients With Chronic Hepatitis C

- Achievement of SVR after treatment is associated with:
 - Improvements in disease progression,
 - Liver histology,
 - Health-related quality of life,
 - Reduced risk of HCC and
 - Liver-related mortality
 -

- **An SVR reduced liver-related mortality among patients with chronic hepatitis C (3.3- to 25-fold),**
- **The incidence of hepatocellular carcinoma (1.7- to 4.2-fold),**
- **Hepatic decompensation (2.7- to 17.4-fold).**

*Vivian NG et al. Clinical gastroenterology and hepatology
2011;9:923–930*

Liver Disease Progression and Hepatic Decompensation in Sustained Viral Responders and Nonresponders

Study	Year	Country	pts	Antiviral used	Mean Foll-up	SVR %	Progression/decompensation SVR	Non SVR
Fibrosis								
Bruno et al.	2001	Italy	47	IFN	8.5	100%	0%	
Shiratori	2000	Japan	487	IFN	3.7	37.6%	1.1%	19.1%
Huang et al.	2007	Taiwan	892	IFN 628,IFN/R264	5	70.6%	3.8%	10.3%
George et al	2008	USA	150	IFN/RBV146 Peg/RBV 4	5	100%	0.7%	
Advanced Fibrosis								
Trapero-Marugan et al	2011	Spain	5	PEG IFN/RBV	6.3	100%	0%	
Iacobellis et al	2007	Italy	61	PEG IFN /RBV	2.5	21.3%	23.1%	68.8%

Liver-Related Mortality in Sustained Viral Responders and

Nonresponders

Study	Year	Country	pts	Antiviral used	Mean Foll-up	SVR %	Liver-related deaths, SVR	Non SVR
All stages of fibrosis								
Arase et al	2007	Japan	500	469 IFN, 31 IFN/RBV	7.4	(28%)	(1.4%)	(8.9%)
Coverdale et al	2004	Australia	343	IFN-alfa	6.81	(14.6%)	(2%)	(8.2%)
Kasahara et al	2004	Japan	2668	IFN	6	(27.7%)	(0.14%)	(3.5%)
Yoshida et al	2002	Japan	2430	IFN	5.4	(33.6%)	(0.24%)	(2%)
Advanced fibrosis								
Morgan et al	2010	USA	526	PEG-IFN/RBV	7.5	(26.6%)	(0.7%)	(6%)
Bruno et al	2007	Italy	920	IFN	8	(13.5%)	(1.7%)	(11.4%)
Braks et al	2007	France	113	35 IFN, 40 IFN/RBV, 38 PEG-IFN/RBV	7.7	(32.7%)	(0%)	(15%)
Mallet et al	2008	France	96	61 IFN, 34 IFN/RBV	9.8	(40.6%)	(8.6%)	(31.1%)
Veldt et al	2007	Mcenter	479	131 IFN, 130 IFN/RB 10 PEG,208PEG/RBV	2.1	(29.6%)	(0.7%)	(7.1%)

Sustained Virological Response to Interferon- α Is Associated with Improved Outcome in HCV-related Cirrhosis: A Retrospective Study

Savino Bruno,¹ Tommaso Stroffolini,² Massimo Colombo,³ Simona Bollani,¹ Luisa Benvegnù,⁴ Giuseppe Mazzella,⁵ Antonio Ascione,⁶ Teresa Santantonio,⁷ Felice Piccinino,⁸ Pietro Andreone,⁹ Alessandra Mangia,¹⁰ Giovanni B. Gaeta,¹¹

Marcello Persico,¹² Stefano Faggioli,¹³ Piero L. Almasio,¹⁴

on behalf of the Italian Association of the Study of the Liver Disease (AISF).

n: 920 SVR: 13.5 % IFN Alpha mono for 1 year . Follow up 8 years

Conclusion :in patients with HCV-related cirrhosis, SVR after IFN therapy is associated with

- A reduction of liver-related mortality**
- Lower rate of complications**
- Lower HCC development.**

- **IFN therapy not only improves hepatic inflammation and fibrosis, but also leads to a reduction in the incidence of HCC, particularly in patients achieving a sustained virological response (SVR)**

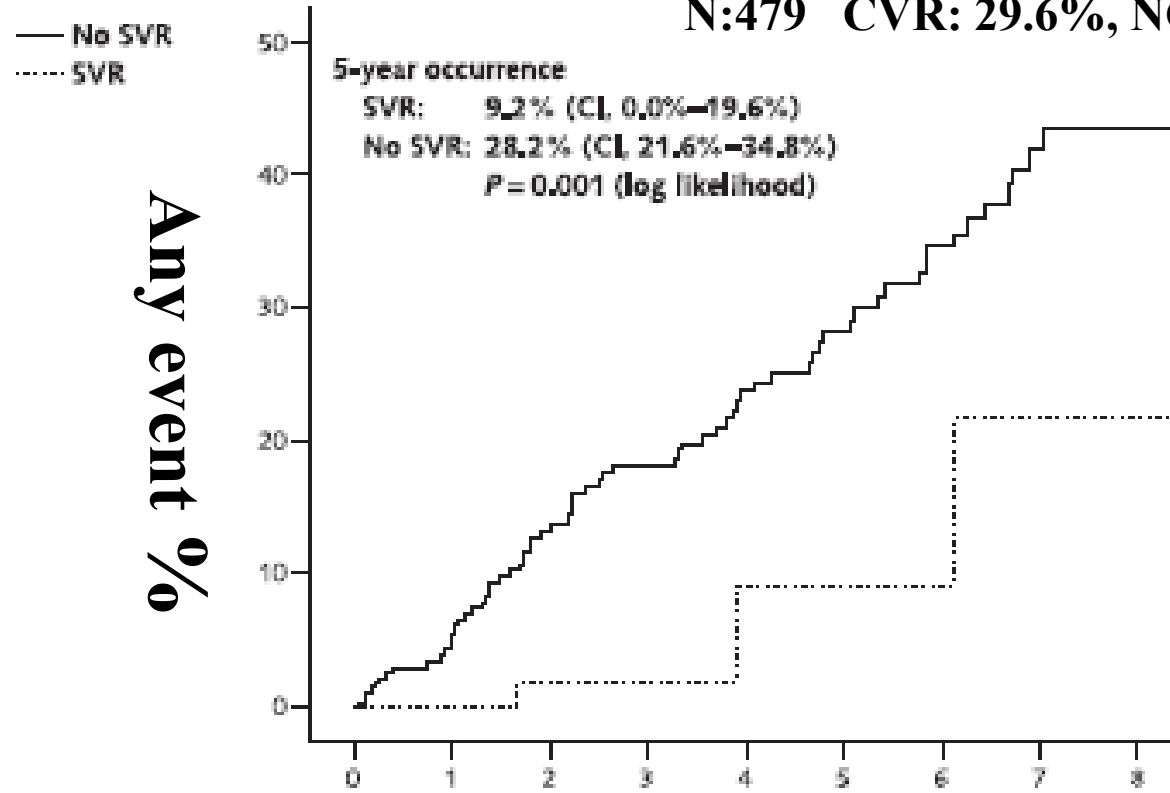
Aleman S et al. Clin Inf Dis 2013; 57: 230-236.

Singal AK et al. Clin Gastroenterol Hepatol 2010; 8: 192-199.

Clinical events in patients with and without (SVR) in HCV pts with advanced fibrosis

Veldt BJ et al *Ann Intern Med.* 2007;147(10):677-684.

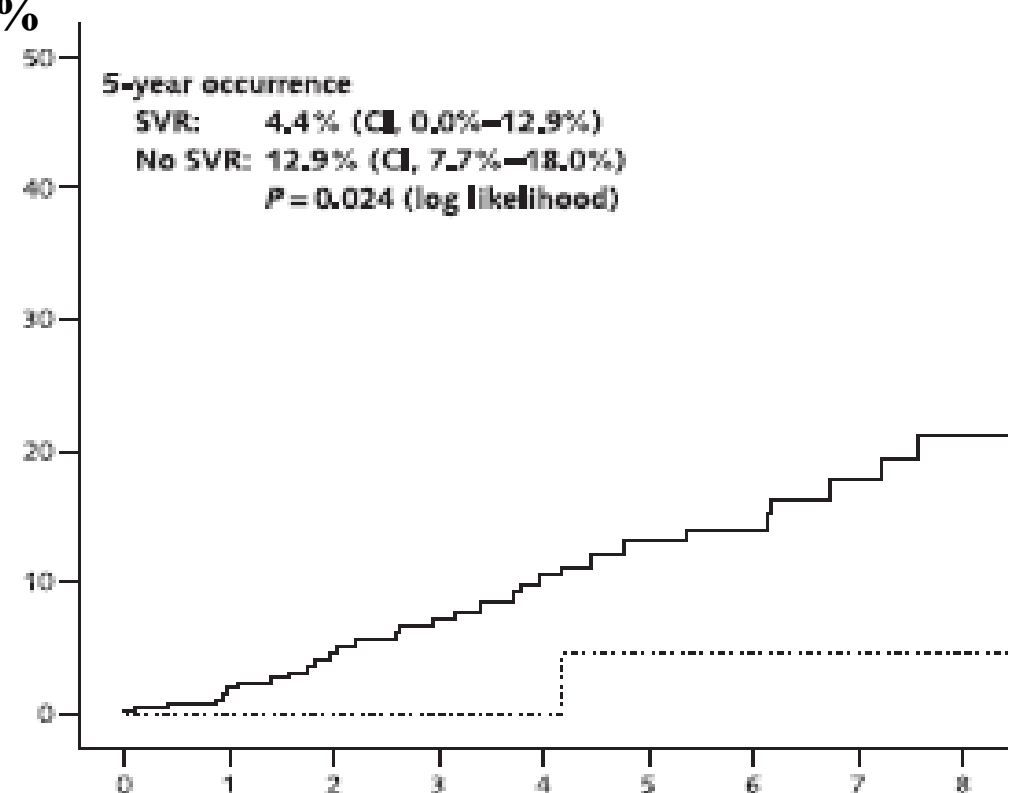
N:479 CVR: 29.6%, NCVR: 70.3 %



Any event %

	Time, y									
No SVR										
At risk	337	254	179	148	114	86	66	38	26	
Events	0	15	34	44	53	59	66	72	73	
SVR										
At risk	142	76	48	35	23	14	8	6	5	
Events	0	0	1	1	3	3	3	4	4	

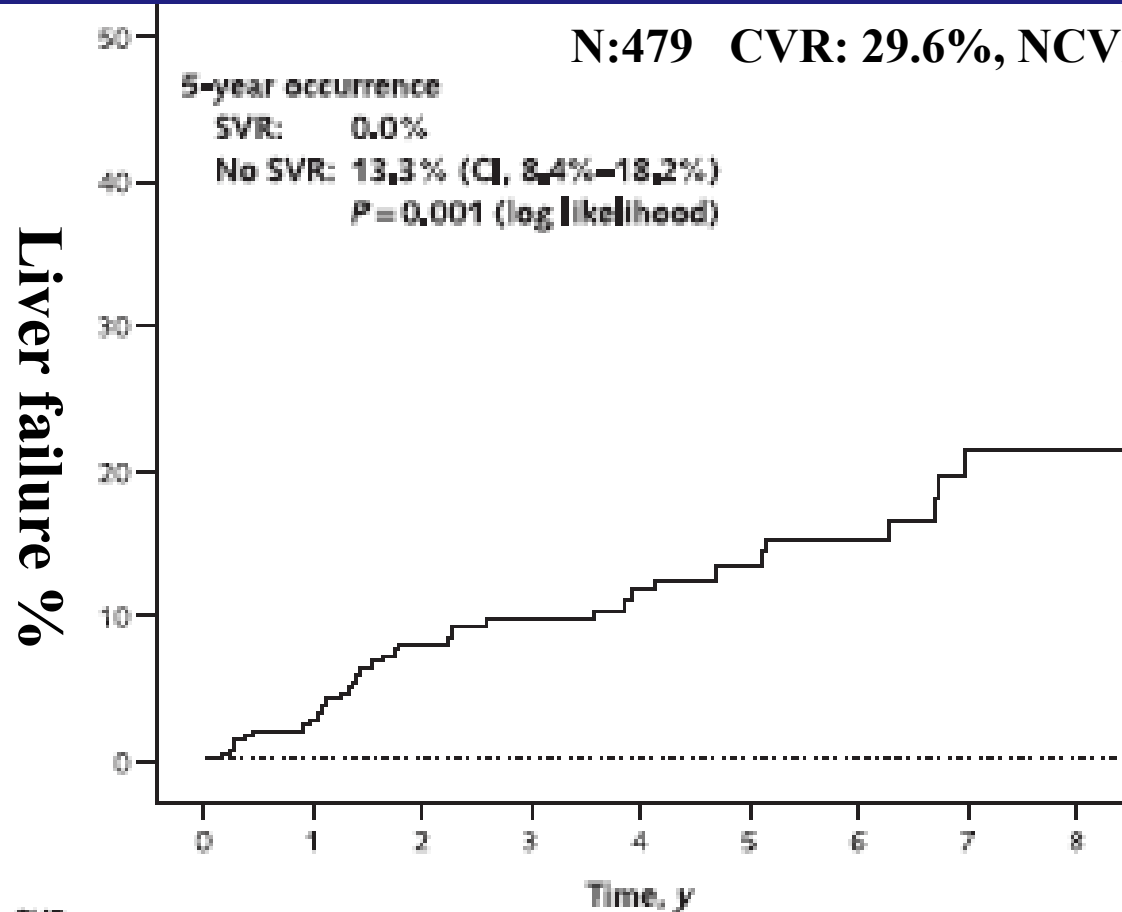
Liver related death %



	Time, y									
No SVR										
At risk	337	261	192	160	124	95	79	49	31	
Events	0	5	11	16	20	24	25	28	30	
SVR										
At risk	142	76	48	35	25	14	8	6	5	
Events	0	0	0	0	0	1	1	1	1	

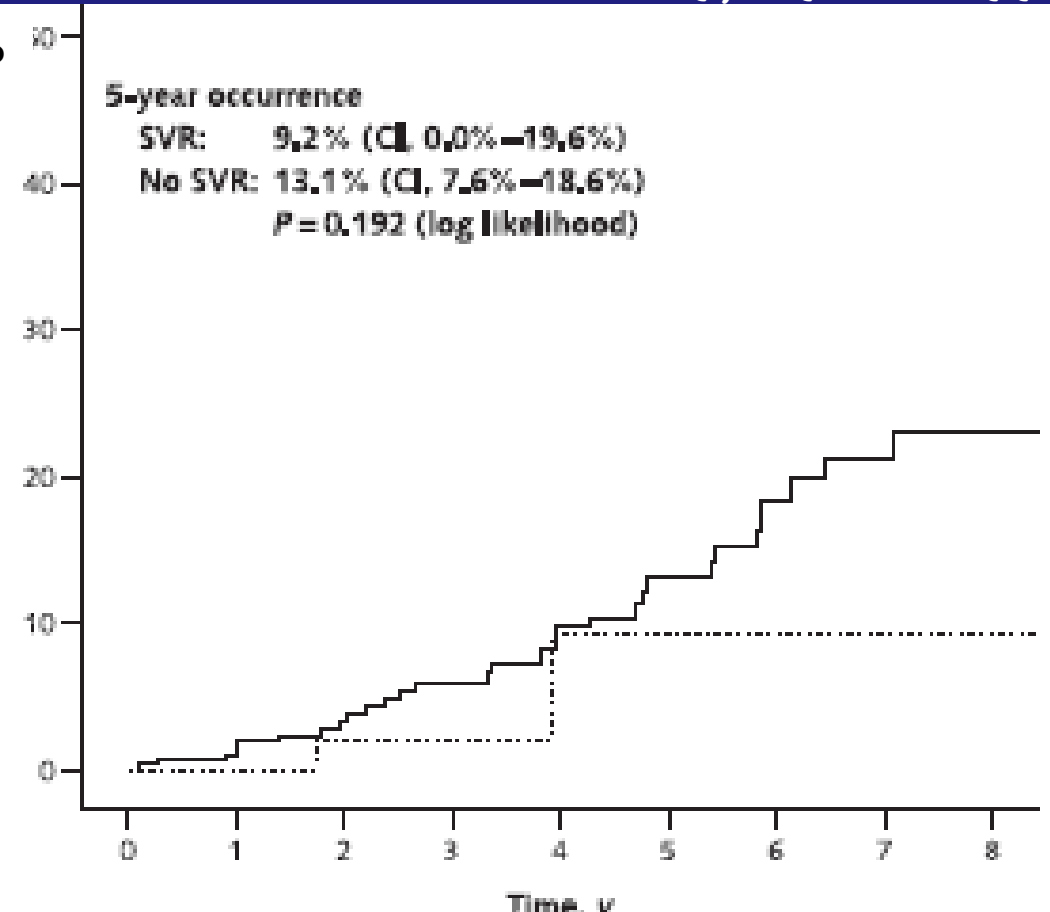
Clinical events in patients with and without (SVR) in HCV pts with advanced fibrosis

Veldt BJ et al *Ann Intern Med.* 2007;147(10):677-



No SVR		0	1	2	3	4	5	6	7	8
At risk		337	256	183	155	121	92	74	44	27
Events		0	8	21	24	27	29	31	35	35
SVR		0	1	2	3	4	5	6	7	8
At risk		142	76	48	35	25	14	8	6	5
Events		0	0	0	0	0	0	0	0	0

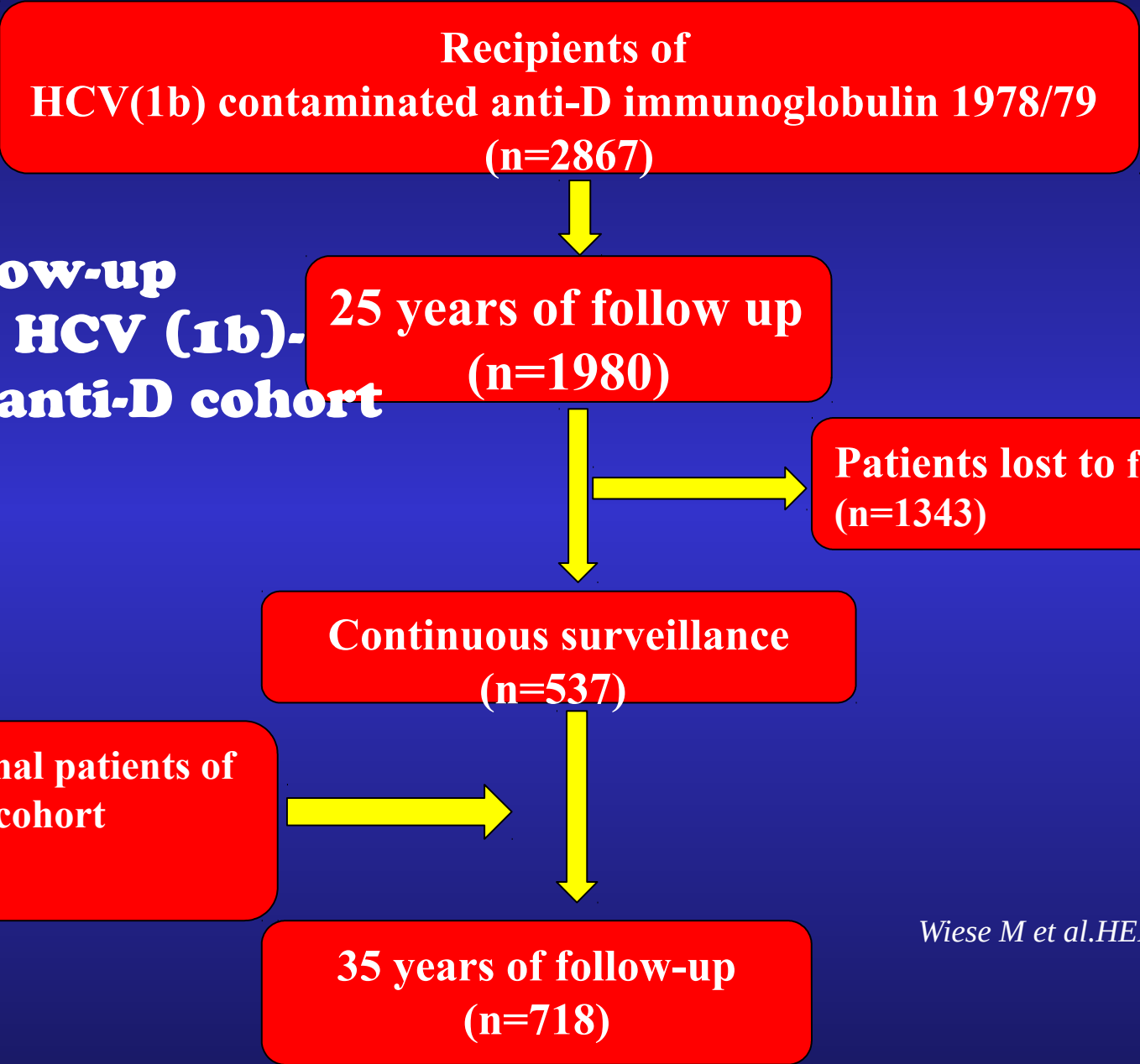
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No SVR		0	1	2	3	4	5	6	7	8
At risk		337	259	188	153	117	90	71	43	30
Events		0	5	8	13	18	22	27	29	30
SVR		0	1	2	3	4	5	6	7	8
At risk		142	76	48	35	24	14	8	6	5
Events		0	0	1	1	3	3	3	3	3

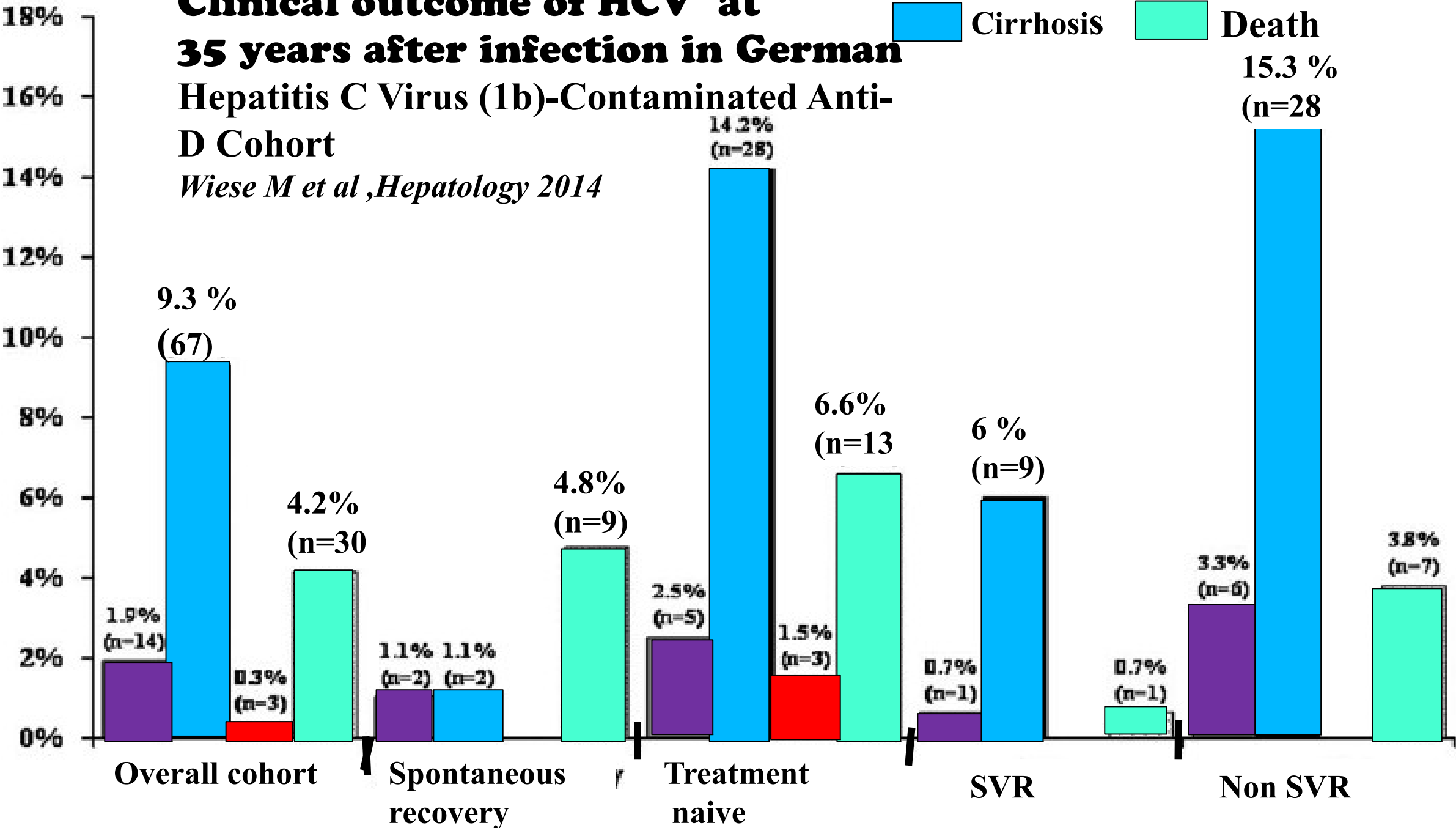
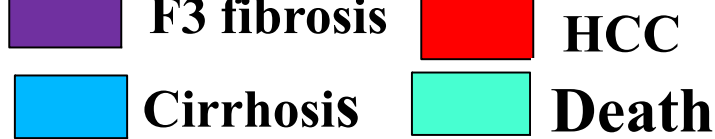


**Long-term follow-up
of the German HCV (1b)-
contaminated anti-D cohort**



Clinical outcome of HCV at 35 years after infection in German Hepatitis C Virus (1b)-Contaminated Anti-D Cohort

Wiese M et al ,Hepatology 2014



After inoculation of HCV

- **9.3% of patients showed clinical signs of liver cirrhosis at 35 years after infection**
- **Those with self limited HCV and those with SVR had less progression to cirrhosis**
- **Obesity and overweight increased the rate of fibrosis progression to cirrhosis and decreased survival in 35 years of follow up**

Effect of IFN on the development of HCC

	Design	Treated (%)	Control (%)
Nishiguchi 95	RCT	4	38*
Mazzella 96	NRCT/P	3	10*
Fattovich 97	NRCT/P	4	12*
Bruno 97	NRCT/P	7	22*
Serfaty 98	NRCT/P	4	23*
IIHCSG 98	NRCT/R	9	19*
Imai 98	NRCT/R	25	35
Benvegnu 98	NRCT/R	5.6	26.7*
Valla 99	RCT	11	15
Ikeda 99	NRCT/R	4.8	12.4*
Inoue 2000	NRCT/R	2.2	9.5*

HCC Occurrence in Sustained Viral Responders and Nonresponders

Study	Year	Country	pts	Antiviral used	Mean Foll-up	SVR %	HCC Occurrence SVR	Non SVR
All stages of fibrosis								
Arase et al ⁴⁰	2007	Japan	500	469 IFN, 31 IFN/RBV	7.4	140/500 (28%)	13/140 (9.3%)	58/360 (16.1%)
Coverdale et al ⁴¹	2004	Australia	343	IFN	6.81	50/343 (14.6%)	1/50 (2%)	23/293 (7.8%)
Tanaka et al ⁶⁸	2000	Japan	594	IFN	4.8	175/594 (29.5%)	3/175 (1.7%)	30/419 (7.2%)
Kobayashi et al ⁶⁹	2007	Japan	1124	1039 IFN, 85 IFN/RBV	5.5	373/1124 (33.2%)	13/373 (3.5%)	61/751 (8.1%)
Hung et al ¹¹	2006	Taiwan	132	IFN/RBV	3.1	73/132 (55%)	5/73 (6.8%)	11/59 (18.6%)
Bruno et al ⁶¹	2007	Italy	920	IFN	8	124/920 (13.5%)	7/124 (5.6%)	122/759 (16.1%)
Advanced fibrosis								
Hirakawa et al ⁷⁰	2008	Japan	1193 ^b	1032 IFN, 161 IFN/RBV	8.3	1193/1193 (100%)	9/1193 (0.75%)	
Mallet et al ⁶⁷	2008	France	96	61 IFN, 34 IFN/RBV, 1 PEG-IFN/RBV	9.8	39/96 (40.6%)	3/39 (8.6%)	14/57 (24.6%)
Cardoso et al ⁷¹	2010	France	307	33 IFN ± RBV, 22 PEG-IFN, 252 PEG-IFN/RBV	3.5	103/307 (33%)	6/103 (5.8%)	40/204 (19.6%)

- **Risk factors for HCC in patients with CHC include male sex, age older than 50 years, co-morbidities and the presence of cirrhosis.**

- **In 97% of patients with CHC, SVR is durable without evidence of disease progression,**
- SVR may be associated with subsequent improvement in portal hypertension and perhaps partial regression of fibrosis as shown by transient elastography
- **Patients with pre-treatment cirrhosis are at continuing low risk for hepatocellular carcinoma**

Koh et al. Aliment Pharmacol Ther 2013; 37: 887–894

- Up to 5%-6 % of patients with SVR may develop HCC on long-term follow up

- *Sato A et al. Japan. Intern Med 2013,*

- *Asahina Y et al. Hepatology 2013*

- *Lok A et al. Gastroenterology 2009*

A retrospective analysis and a prospective study of patients followed up for 6.8 years conducted in Japan showed that HCC risk was reduced, but **not abolished**, in patients with cirrhosis

Yoshida H et al., Ann Intern Med 1999;131:174-181

Impact Of Peginterferon And Ribavirin Therapy on Hepatocellular Carcinoma: Incidence And Survival In Hepatitis C Patients With Advanced Fibrosis

- **307** chronic HCV patients with bridging fibrosis (n = 127) or cirrhosis (n = 180) treated with IFN (different regimens) and followed for **3.5** years were analysed
- **33%** achieved SVR
- **non-SVR patients had**
 - 4.72 fold higher rate of HCC
 - 6.70 fold higher rate of liver-related complications and
 - 6.10 fold higher rates of liver-related death than SVR patients

IMPACT OF PEGINTERFERON AND RIBAVIRIN THERAPY ON HEPATOCELLULAR CARCINOMA: INCIDENCE AND SURVIVAL IN HEPATITIS C PATIENTS WITH ADVANCED FIBROSIS

Cardoso et al. J Hepatol 2010;52:652–657.

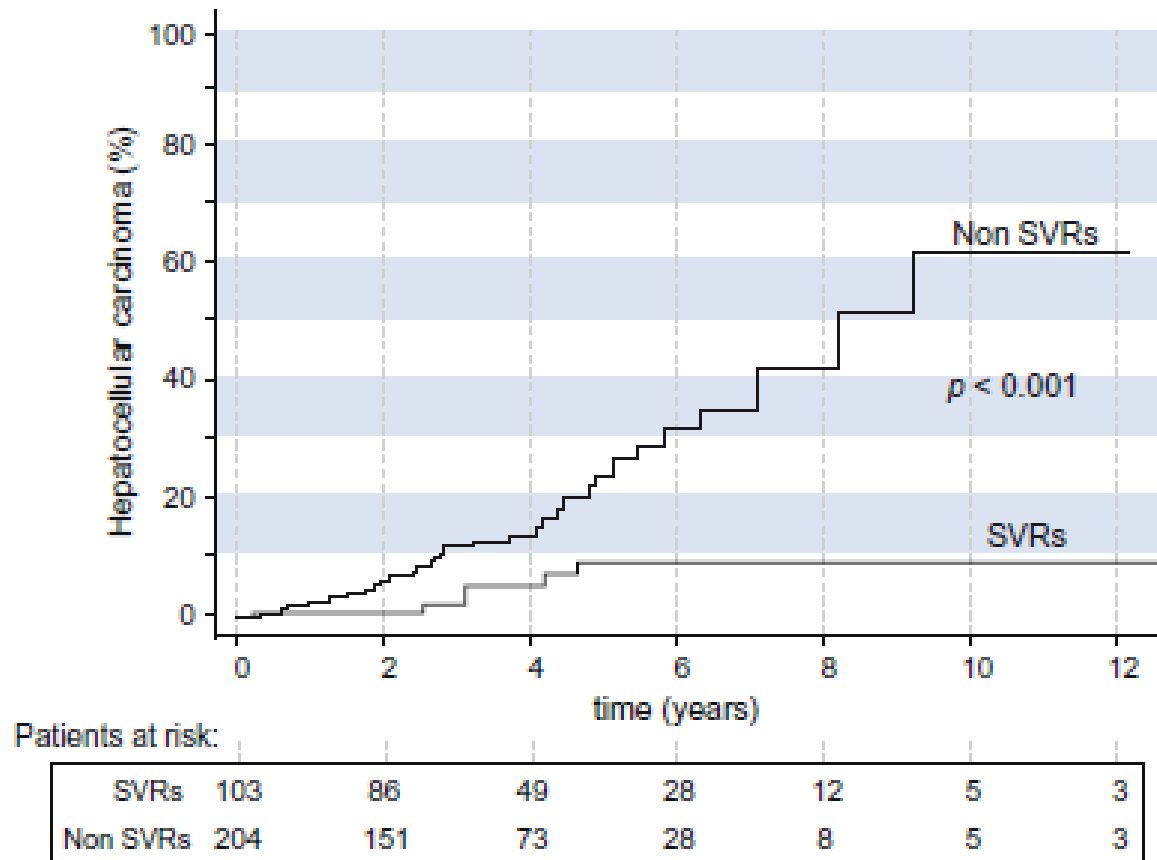


Fig. 1. Cumulative incidence of hepatocellular carcinoma stratified according to response to treatment ($p < 0.001$, by log-rank test). SVR, sustained virological response.

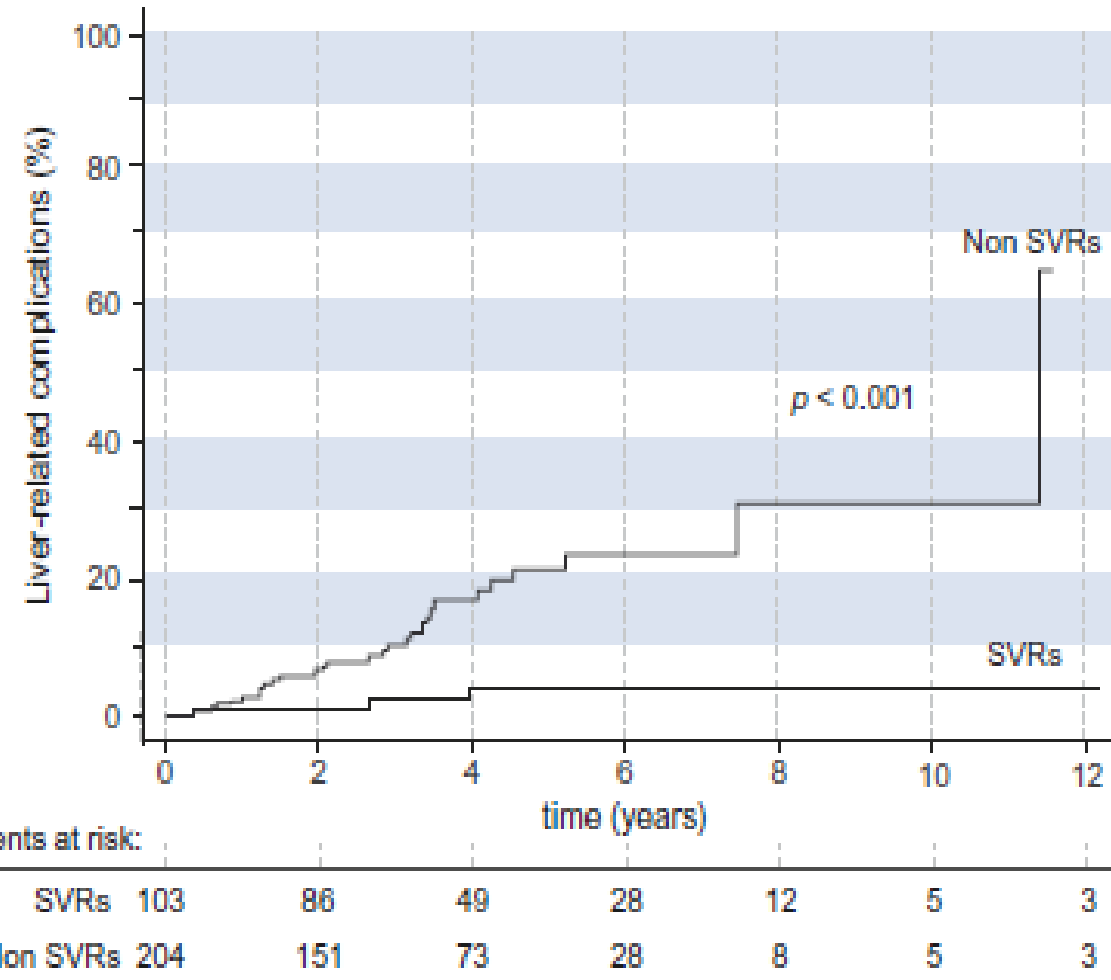


Fig. 2. Cumulative incidence of liver-related complications stratified according to response to treatment ($p < 0.001$, by log-rank test). SVR, sustained virological response.

Why HCC may still develop despite SVR

- Patients with advanced fibrosis /cirrhosis
- Concomitant diseases (diabetes, NAFLD,ASH)
- Small HCC present before SVR

WITH CHRONIC HCV INFECTION AND ADVANCED HEPATIC FIBROSIS FOLLOWING SVR

- The risk of HCC was associated with:
 - Age (patients 45-60 & >60 had 8-9 times increased risk for developing HCC compared to patients <45)
 - Severity of liver disease
 - Diabetes mellitus'

Continued HCC surveillance among patients with cirrhosis and SVR is recommended

-

OTHER BENEFITS OF HCV TREATMENT ?

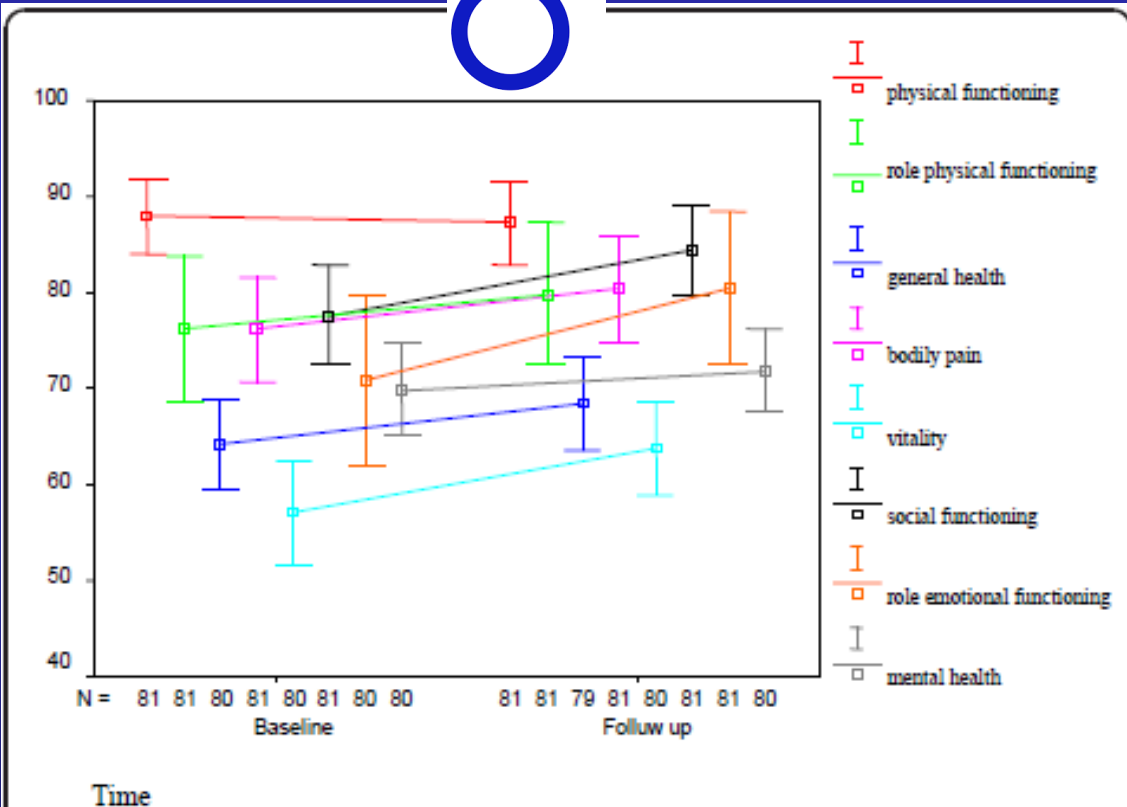
Cognitive Functions Improve After Successful Viral Eradication

Significant improvement in neurocognitive function was observed 12 months after the end of successful viral eradication with pegylated α -interferon-2b and ribavirin

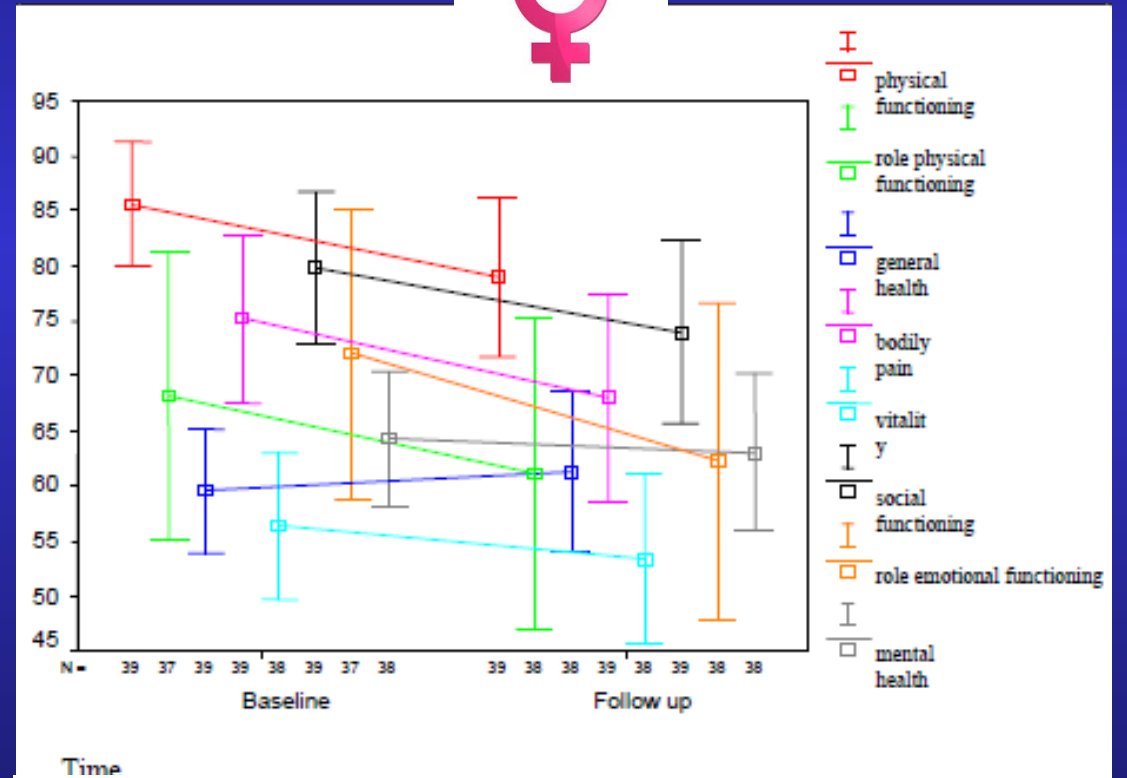
Kraus MR et al. HEPATOLOGY 2013;58:497-504.

Health Related Quality of Life (HRQL) improves with Treatment in Chronic HCV

Bezemer et al. *BMC Gastroenterology* 2012, 12:11
DITTO study group



SF-36 in MALES at **baseline** and at **24 weeks after** completion of treatment (follow up).



SF-36 in FEMALES at **baseline** and at **24 wks after** completion of treatment (follow-up).

HRQOL is influenced by

- **Presence of cirrhosis**
- **Age,**
- **Gender,**
- **Country (cross cultural differences)**
- **Response to treatment.**
- **Awareness of response status to therapy**



Conclusions

- There is beneficial effect of viral clearance in HCV patients on progression of liver disease, decompensation, mortality and HCC development
- HCC may still develop in responders at all stages of fibrosis but especially in pts with advanced fibrosis and cirrhosis
- People at risk should undergo surveillance for HCC even after SVR
- With the availability of newer and more effective therapies, SVR rates can be increased and HCC incidence rates can be reduced in HCV-infected persons

I'M AN INCURABLE OPTIMIST!

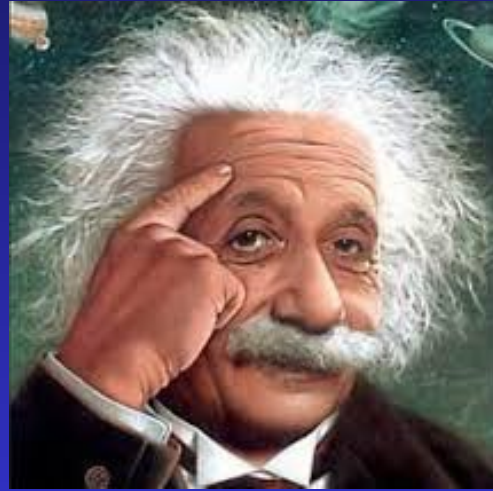
Everything is going well!
Opportunities are many!
The world is great!
It's going to happen!
I am a winner!
I will fulfil my dreams!
Something wonderful is going to take place!
Everything is fine!
I am a success!



© RICHARD DUSZCZAK

Incurable optimism better than dark pessimism

- **Better results expected from newer treatments**
- **Access to treatment and affordability is crucial**
- **Early diagnosis= Better outcome**
- **Molecular prediction of cancer risk /genomic profiling**
- **Identification of patients at risk for HCC and in the need of surveillance after SVR**



*“Intellectuals solve problems;
geniuses prevent
them.”*