Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study

Viral Hepatitis Prevention Board
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Université de Paris

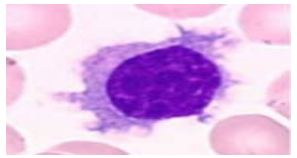
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Disclosures

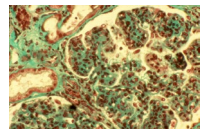
Speaker or **Board member** Gilead, Abbvie, Pfizer, Vivv, NovoNordisk, LFB

Grants : Gilead, Abbvie

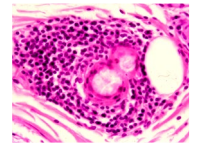
HCV chronic infection is a systemic disease



Lymphoma

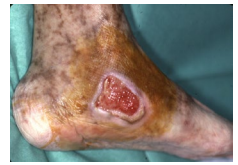


Vasculitis



10%

Cryoglobulinemia



40%

Lymphotropism

Vasculitis

Contamination

Acute Hepatitis

< 35%

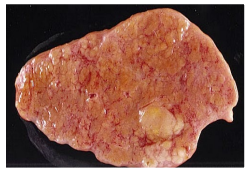
Recovery

> 65%

Chronic Infection

> 95%

Chronic Hepatitis



HCC

> 20%

Cirrhosis

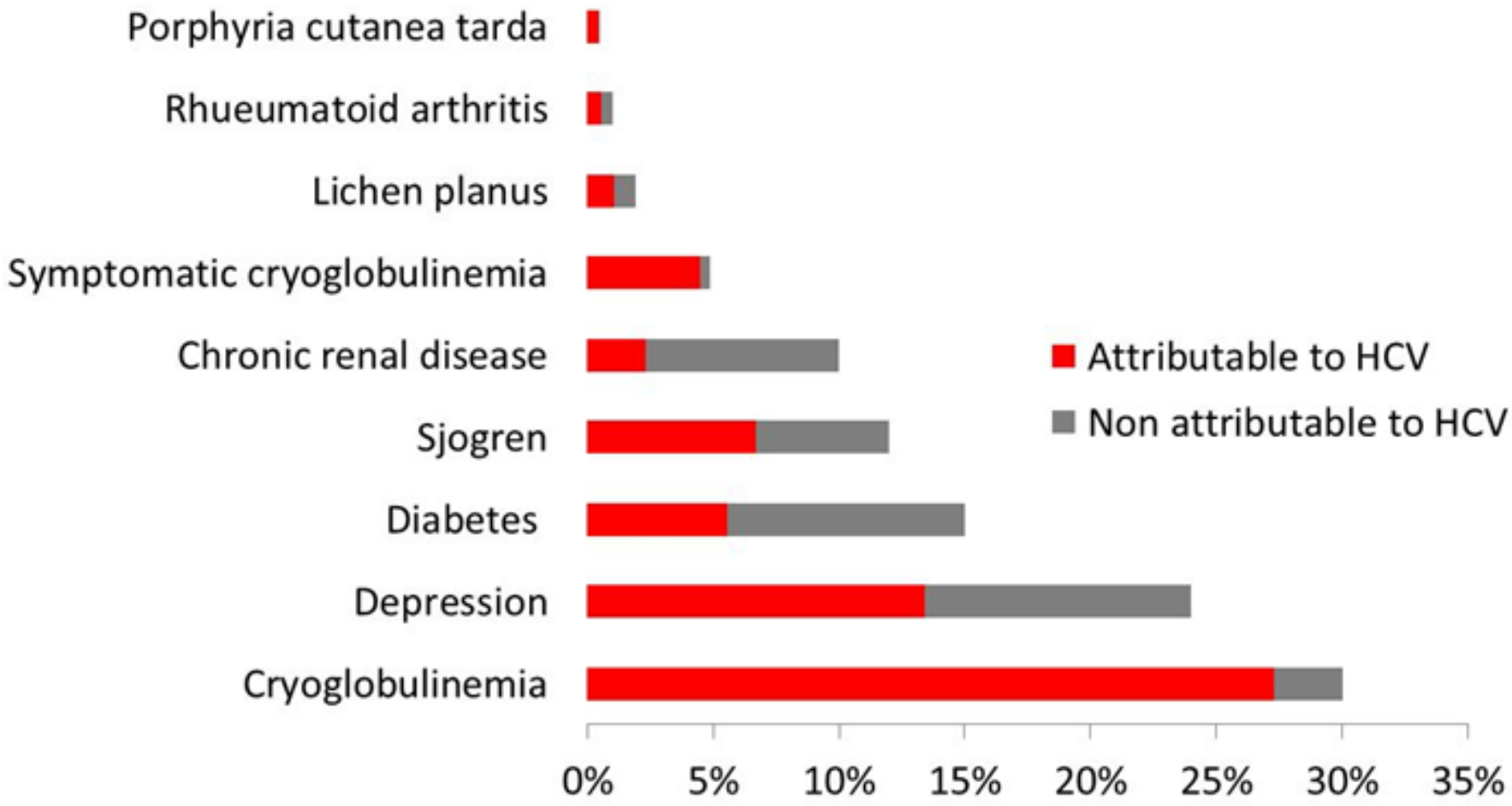
Liver disease

Chronic inflammation

T2D/vascular, neurocognitive dis./cancers

Pol S et al. Nature Rev Nephrol 2019

Prevalence of extra-hepatic manifestations in HCV



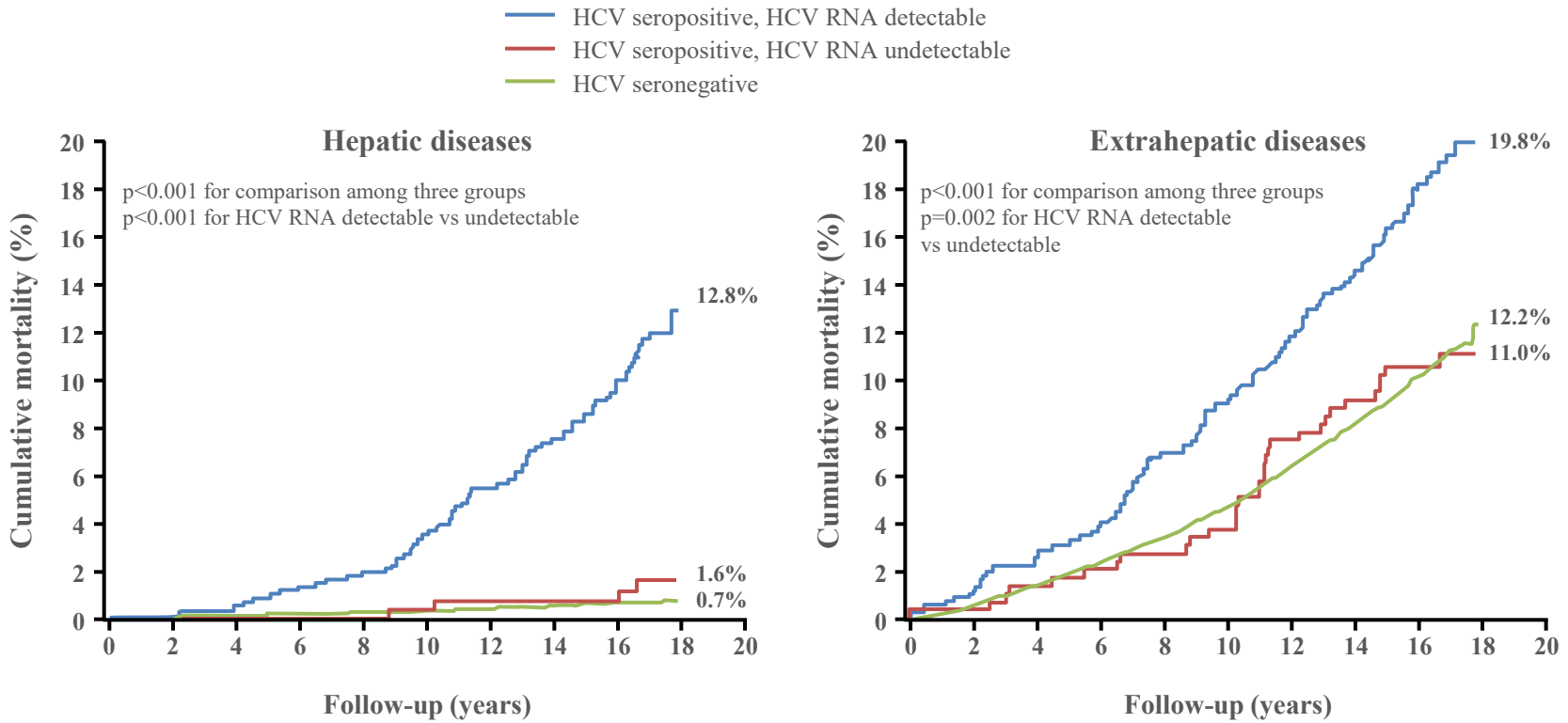
Younossi Z et al, Gastroenterology 2016; WHO 2018,

Chronic HCV infection increases hepatic and non-hepatic mortality

The REVEAL HCV Cohort Study

23 820 adults, Taiwan

1095 anti-HCV positive; 69.4% with detectable HCV RNA



Lee M-H et al, *J Infect Dis* 2012;206:469–477

EASL: treat any viremic patient

ARTICLE IN PRESS JOURNAL OF HEPATOLOGY

Clinical Practice Guidelines

EASL Recommendations on Treatment of Hepatitis C 2018☆

European Association for the Study of the Liver*

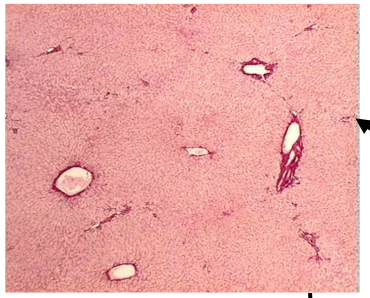
All patients with HCV infection must be considered for therapy, including treatment-naive patients and individuals that failed to achieve SVR after prior treatment

Treatment should be considered without delay in patients with:

- **Significant fibrosis or cirrhosis**
- **Significant EHMs**
- **HCV recurrence after liver transplant**
- **A risk of rapid evolution of liver disease**
- **A risk of infecting others**

EASL Recommendations on Treatment of Hepatitis C, 2018. Available at: http://www.easl.eu/research/

Cure acute and chronic HCV infection



Normal liver

Recovery

Time to treat

Acute Hepatitis

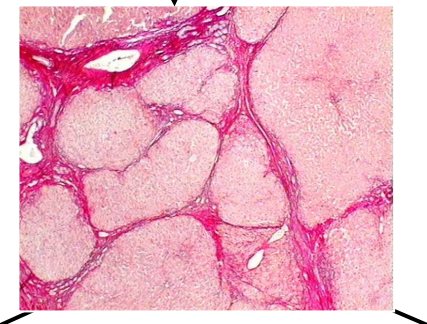
HCV Cure

HCV

Chronic hepatitis

Progression of fibrosis

Liver comorbidities



cirrhosis

3-5%/year

3-5%/year

Decompensation
Ascitis
Digestive bleeding
Hepatic enkephalopathy

Liver cancer
Hepatocellular carcinoma
Cholangiocarcinoma

Death or liver Tx

EASL Recommendations on Treatment of Hepatitis C, 2018. Available at: http://www.easl.eu/research/

Benefits associated with SVR

- Community benefits associated with SVR : reduction of the contagiosity

- Individual benefits associated with SVR :

- Hepatic

- Extrahepatic

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Immediate Treatment for HCV Infections in MSM and PWID

Incidence of HCV Transmission in MSM[1,2]

Doubling time of the HCV epidemic in MSM:[*,1]

0.44 years

With a significant amount of transmission in the acute phase of infection

Modeling indicated that annual screening and **immediate treatment** could reduce HCV incidence by[†,2]:

70%

Incidence of HCV transmission in young PWID[3]

Modeling indicated that treating 3 per 100 PWID could reduce:

Chronic HCV incidence by **27.3%**

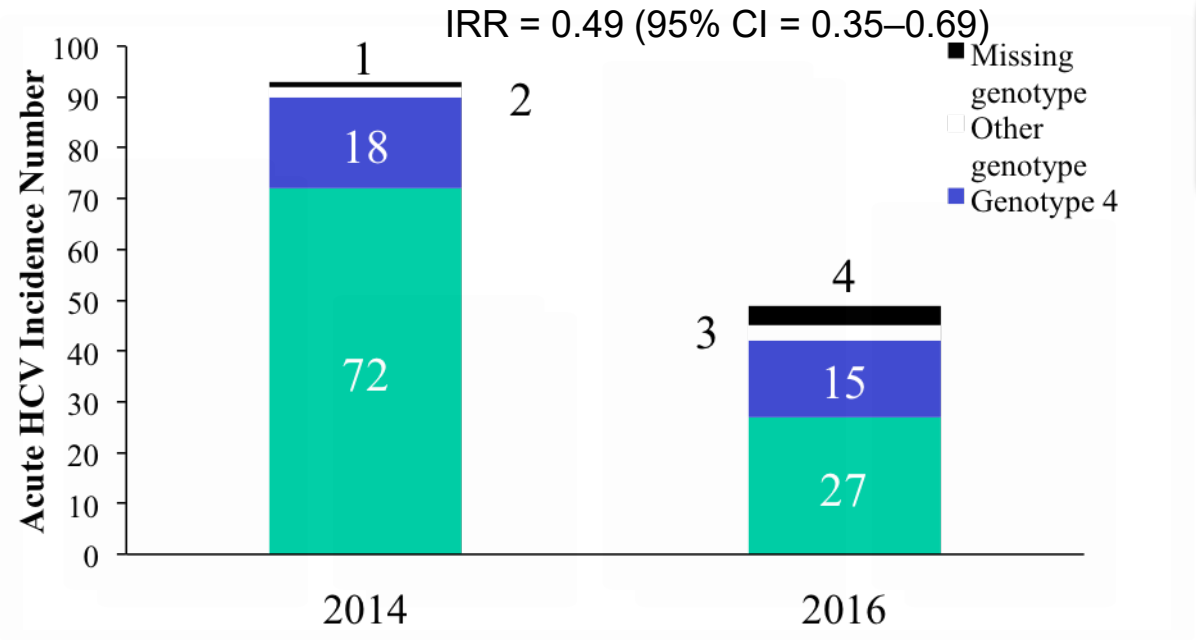
Acute HCV incidence by 23.6%

* Phylodynamic analysis was done using Approximate Bayesian Computation and an original transmission model;
† Model HCV incidence based on 2014 and 2017 incidence.
IDU, injecting drug use; MSM, men who have sex with men; PWID, people who inject drugs.

1. Danesh G, *et al. PLoS Pathog* 2021; **17**:e1009916;
2. Castry M, *et al. Gut* 2021; **70:**1561–1569;
3. Gicquelais R, *et al. Epidemics* 2019; **27:**86–95.

Decreasing HCV infection rate in the Dutch HIV+ MSM community

Retrospective analysis of two prospective studies from the DAHHS to evaluate the effect of introducing interferon-free DAAs for the treatment of chronic HCV in the Netherlands



A 51% decrease in acute HCV infections was observed between 2014 and 2016

Positive syphilis (from 6.6% to 8.4%,*P* = 0.001) and gonorrhea (from 16.4% to 19.2%, *P* < 0.001) test results increased from 2014 to 2016

Unrestricted DAA HCV therapy availability has been associated with a decreased HCV infection rate among HIV-positive MSM

DAHHS, Dutch Acute HCV in HIV Studies; IRR, incidence rate ratio; MSM, men who have sex with men.

Boerekamps A, et al. Clin Infect Dis 2018; 66:1360–1365

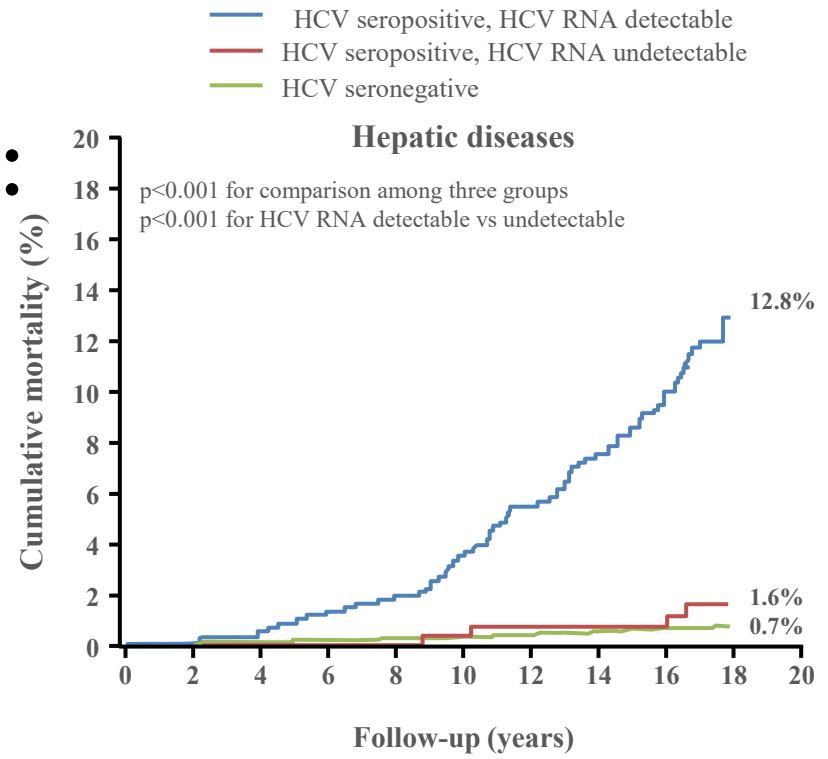
Benefits associated with SVR

- Community benefits associated with SVR : reduction of the contagiosity

- Individual benefits associated with SVR :

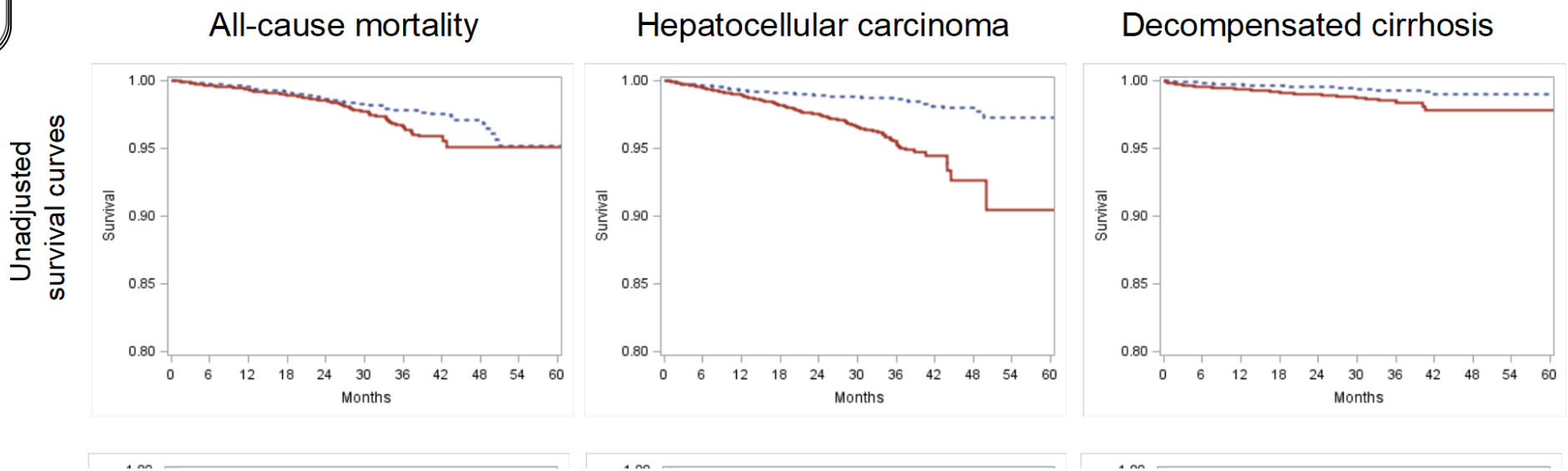
• Hepatic

• Extrahepatic



CO22
HEPATHER

Benefits associated with SVR



DAA+ DAA-

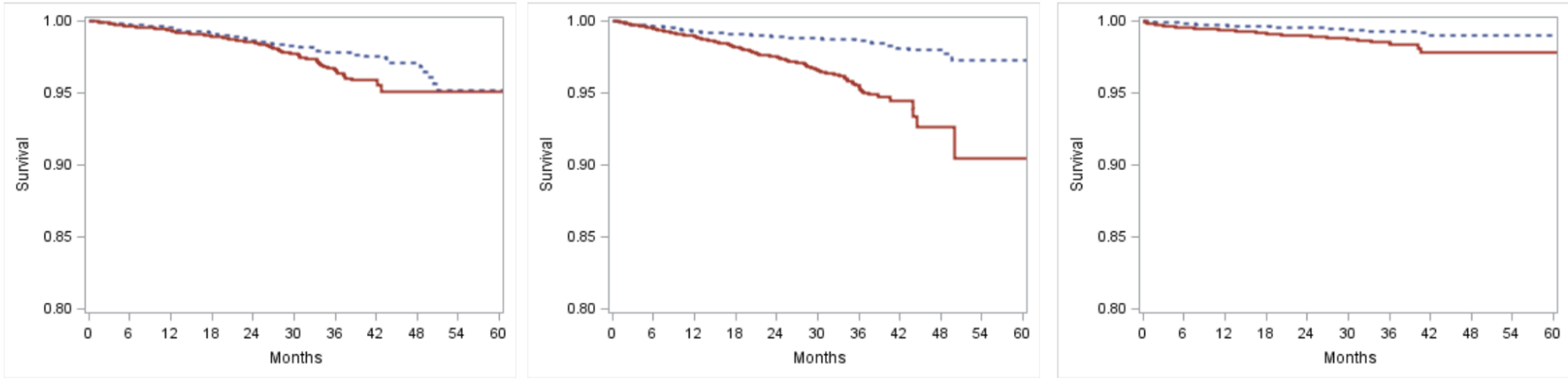
Carrat F et al. The Lancet 2019

CO22
HEPATHER

Benefits associated with SVR

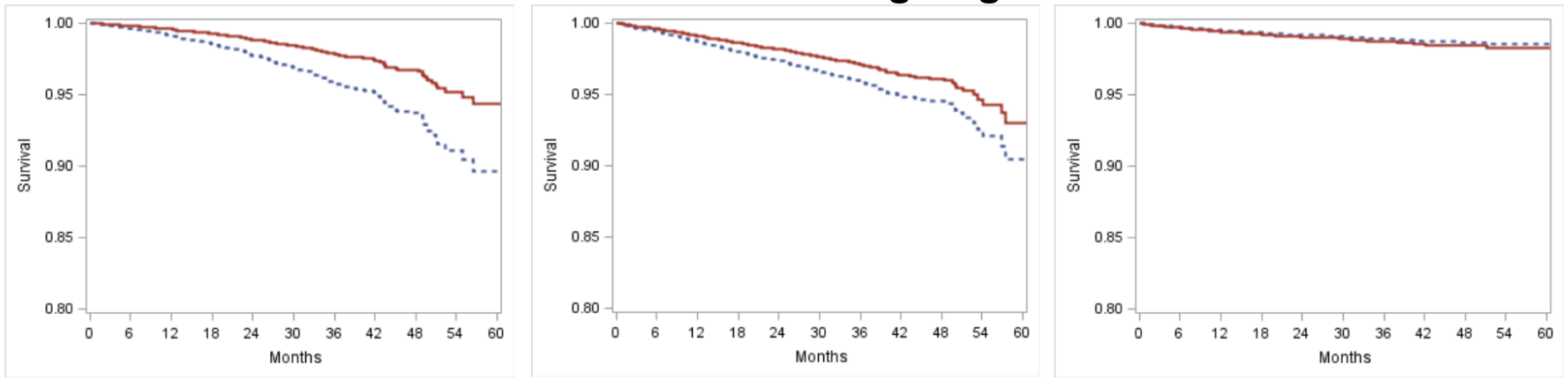
All-cause mortality | Hepatocellular carcinoma | Decompensated cirrhosis

Unadjusted survival curves



Pseudo-survival curve with IPTW weighting

Multivariate-adjusted survival curves



	Months	0	12	24	36	48	60
N at risk	DAA+	7344	5448	3469	1012	59	6
	DAA-	9895	4774	2889	1344	360	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

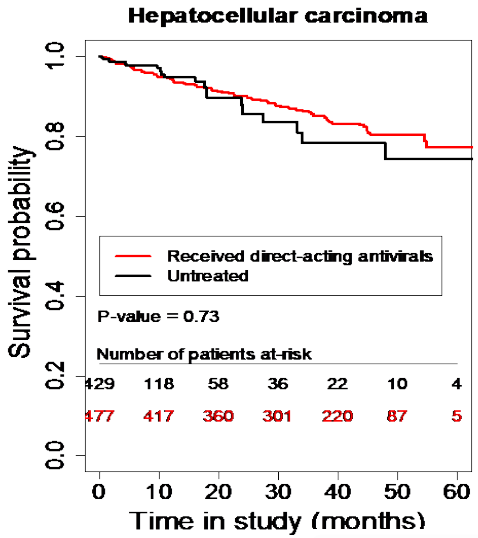
	Months	0	12	24	36	48	60
N at risk	DAA+	7330	5408	3432	996	59	6
	DAA-	9895	4766	2888	1342	360	10

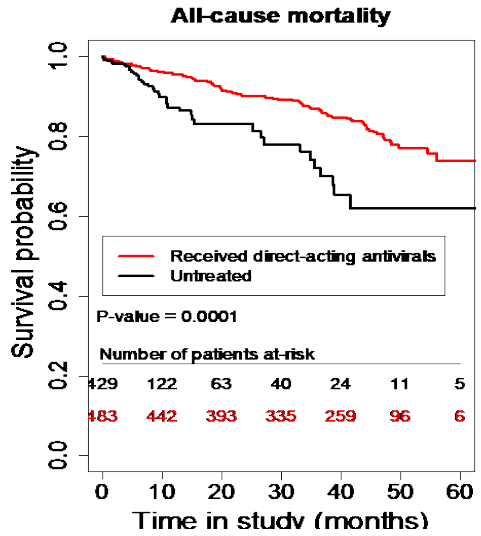
DAA+ DAA-

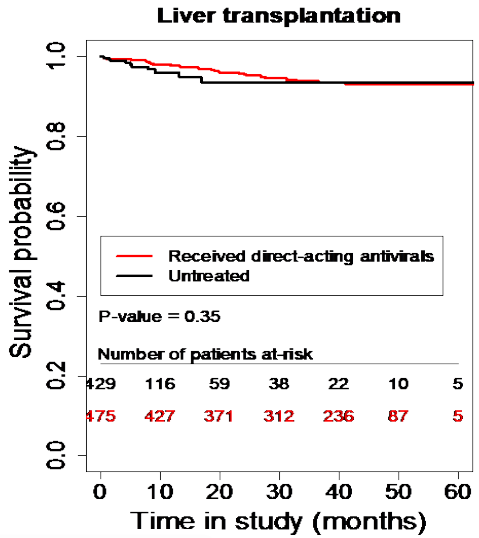
Carrat F et al. The Lancet 2019

CO22
HEPATHER

Benefits associated with SVR in decompensated cirrhosis







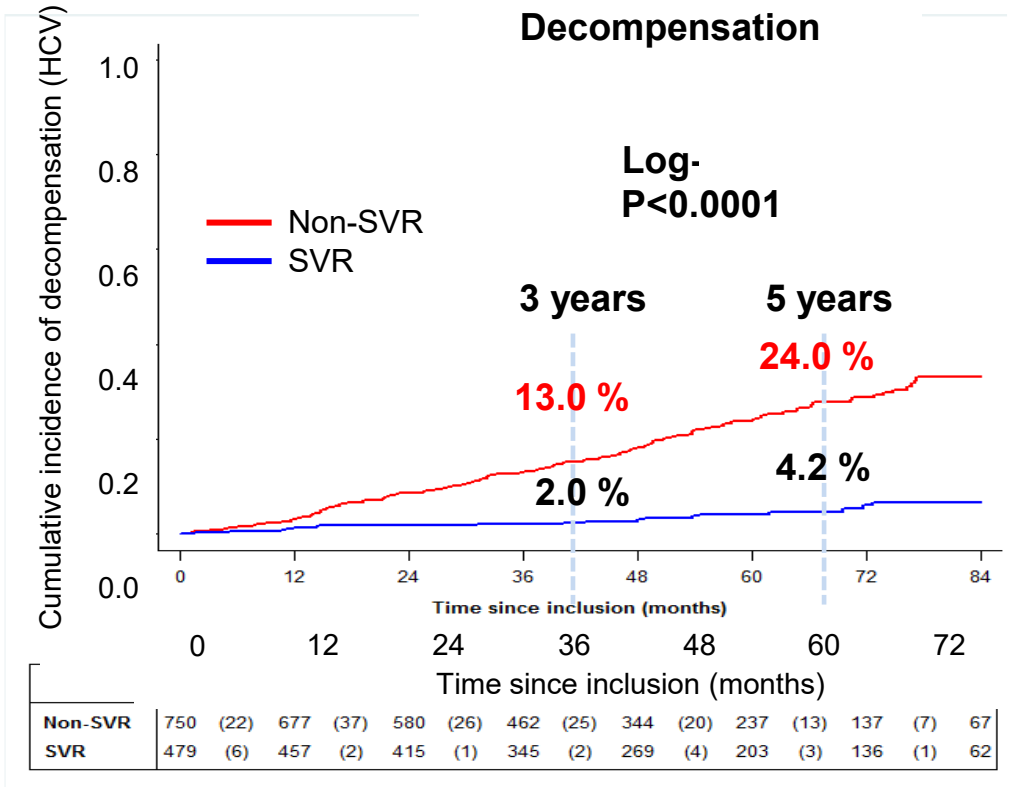
Patients with
a MELD score > 20

	Not exposed to DAA		Exposed to DAA		P-value
	n/pyrs	Incidence/100 pyrs (95%CI)	n/pyrs	Incidence/100 pyrs (95%CI)	
HCC	7/22	31.2 (12.5-64.3)	4/100	4.0 (1.1-10.3)	**0.001**
All-cause mortality	10/26	38.5(18.5-70.8)	10/112	9.0 (4.3-16.5)	**0.002**
Liver transplant	4/20	20.0(5.5-51.3)	5/92	5.4 (1.8-12.7)	0.07

Pageaux GP, et al. BMC Infectious Dis 2022

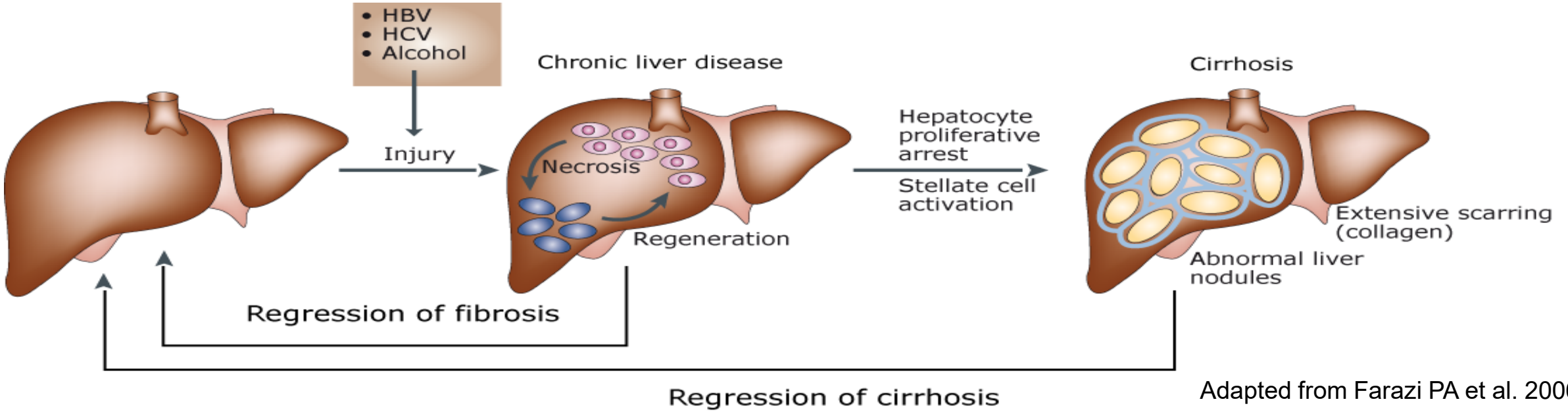
CO20 CIRVIR

Benefits associated with SVR in cirrhotics

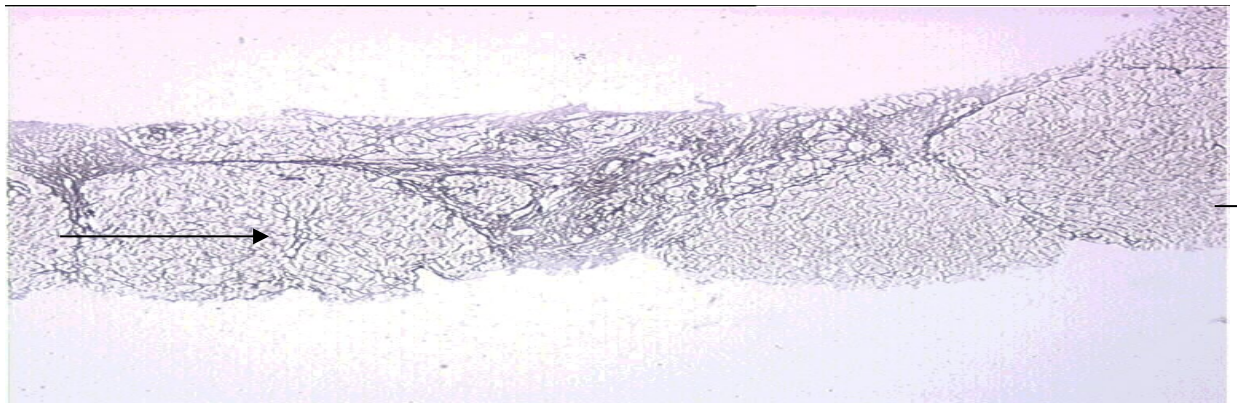


Nahon P et al. Gastroenterology 2017

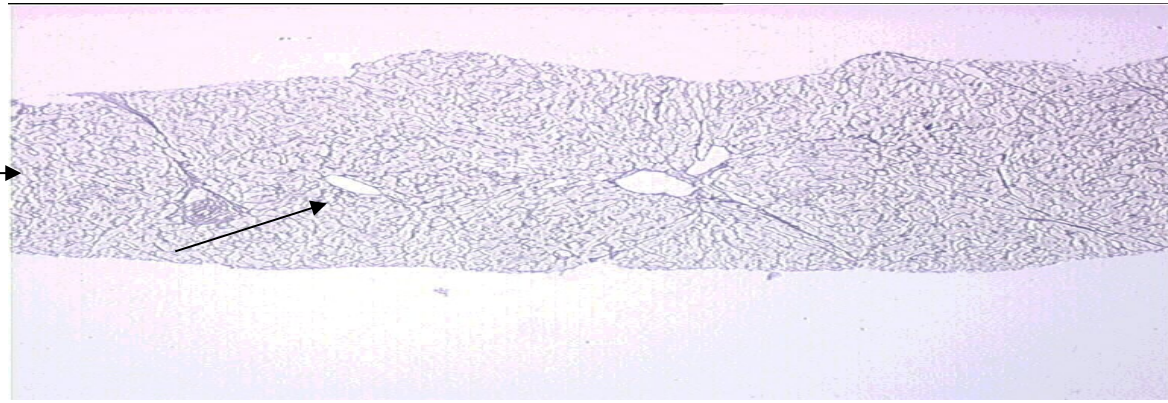
Pathobiology of fibrosis/cirrhosis regression



Adapted from Farazi PA et al. 2006



HCV cure

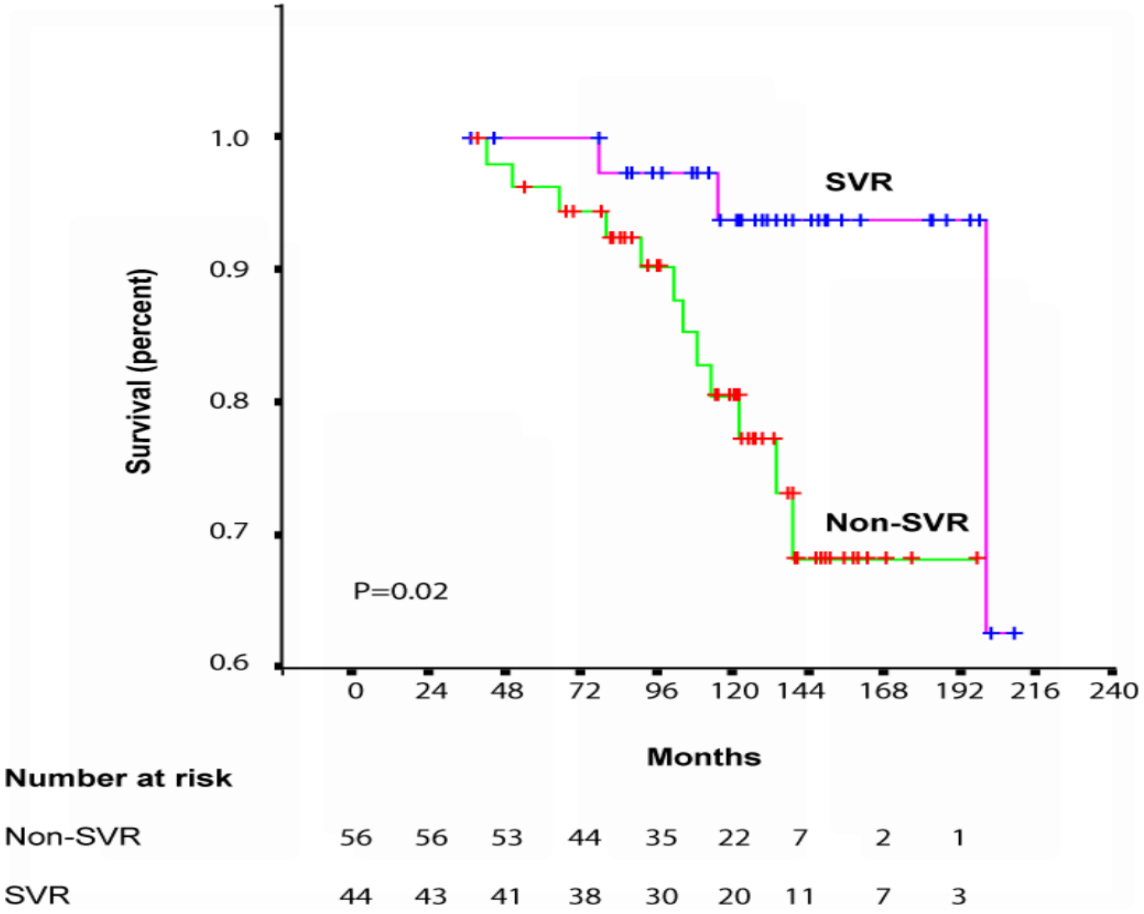


Pol et al. Human Pathology 2004

Impact of fibrosis/cirrhosis regression

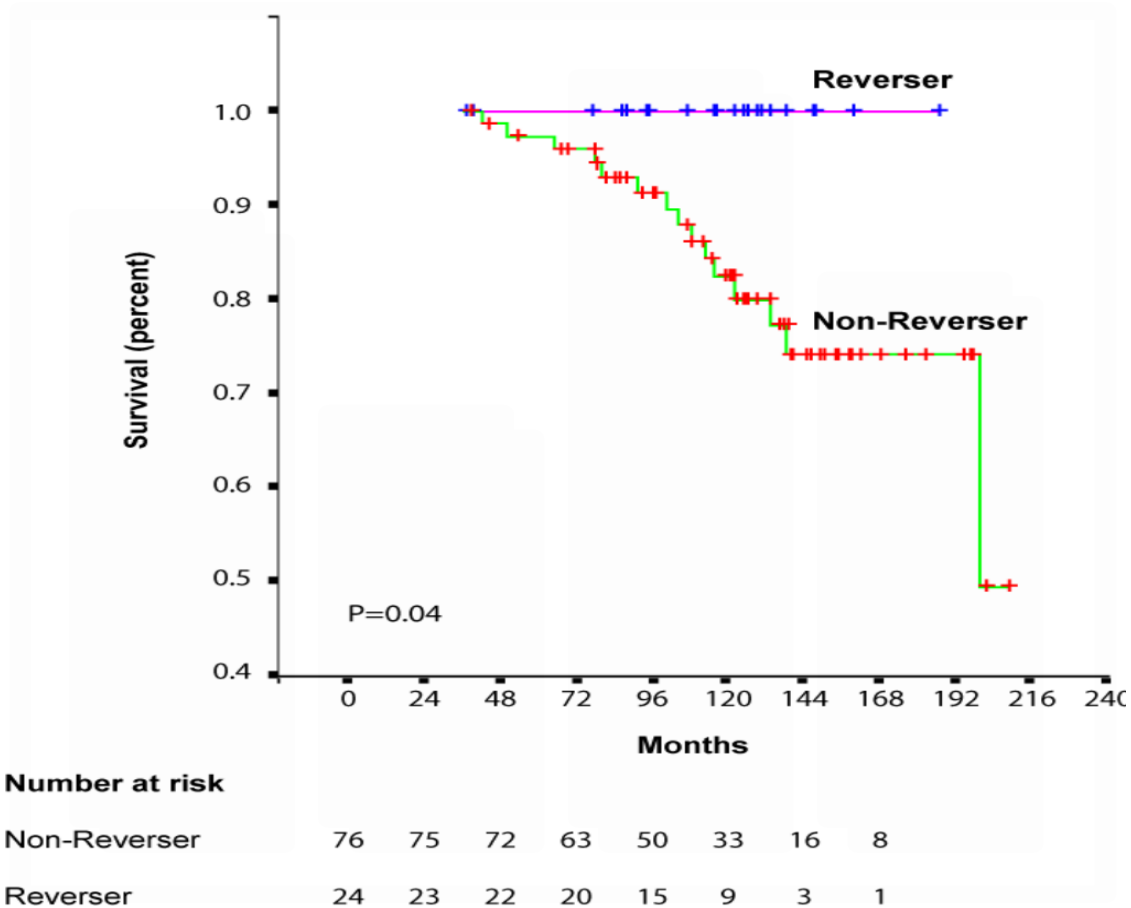
Overall survival: death or liver transplantation

Stratified on viral-response



Number at risk									
Non-SVR	56	56	53	44	35	22	7	2	1
SVR	44	43	41	38	30	20	11	7	3

Stratified on histological response



Number at risk								
Non-Reverser	76	75	72	63	50	33	16	8
Reverser	24	23	22	20	15	9	3	1

Mallet et al. Ann Intern Med 2008

SVR improves survival after a 1st HCC

CirVir CO12

Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts

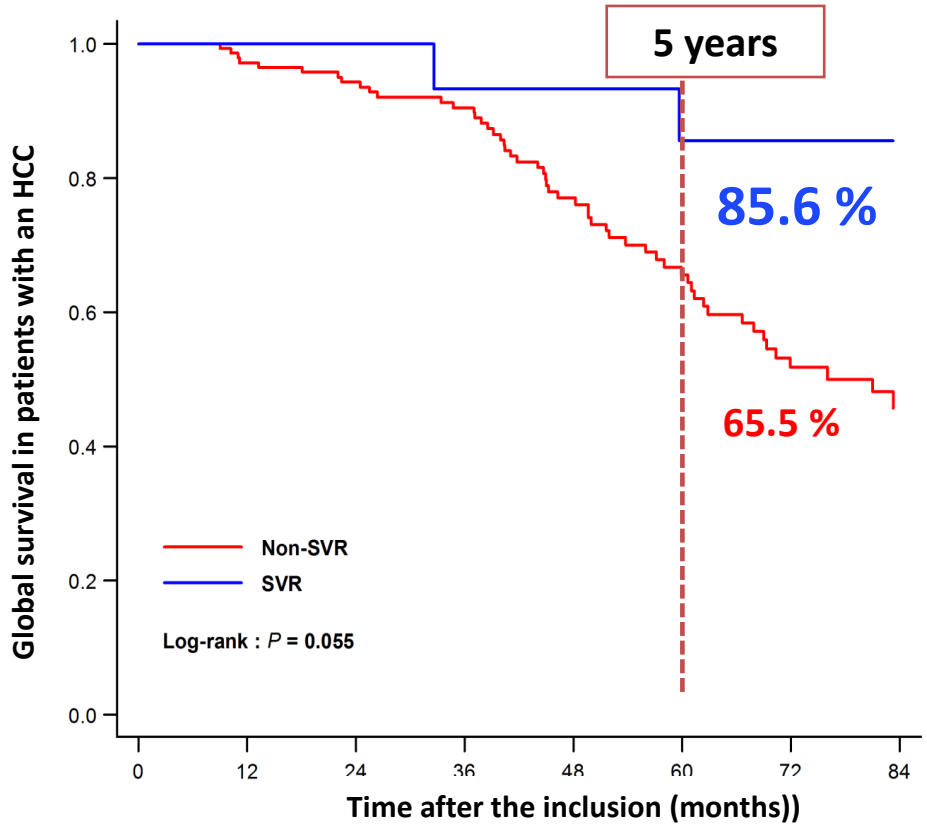
The ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts)*

l'Agence de recherche ANRS (France REcherche Nord&Sud Sida-HIV Hépatites), Paris, France

JHEPAT 6143 ARTICLE IN PRESS No. of Pages 8
11 July 2016

Research Article

JOURNAL OF HEPATOLOGY



	At-risk patients (events)														
Non-SVR	142	(4)	138	(4)	127	(5)	115	(16)	81	(11)	57	(11)	36	(3)	18
SVR	17	(0)	17	(0)	15	(1)	14	(0)	13	(1)	11	(0)	9	(0)	4

	No SVR (n = 55)	SVR (n = 3)
Absence of progression of CHC	28 (51)	3 (100)
Liver insufficiency	13 (24)	0
Extra-hepatic events	14 (25)	0

Nahon et al. Gastroenterology 2016; Pol S et al. J Hepatol 2016

SNDS

Impact of DAA on liver transplantation in HCV-related HCC

- Analysis between 2013 and December 2021 with or without DAA (time-dependent variable) after diagnosis of HCC
- Outcome: liver transplantation
- 4760 patients with HCV-related HCC: 415 liver transplantations (8.7%) during follow-up with an incidence of:
  - 35/1000 persons-year for the period without DAA exposure and
  - 34/1000 persons-year for the period with DAA exposure

Adjusted HR = 1.05 (IC 95%, 0.83, 1.32), p = 0.70

No impact of DAA on the liver transplantation access in patients with HCV-related HCC

Work in progress. Pol S, Mouliade C, Lam L, Carrat F. 2025

SNDS

Impact of DAA before liver transplantation in HCV-related HCC

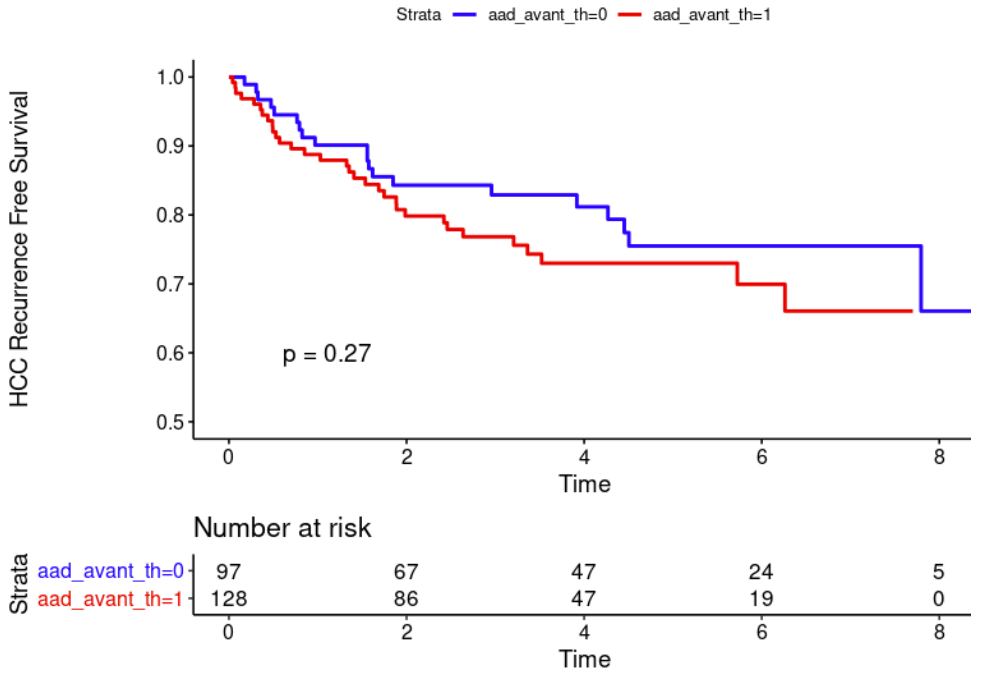
Outcome: **relapse of pos-LT HCC**

225 patients (LT between 2013 & 2021): 52 HCC relapses

Post-LT HCC relapse: DAA+ : 77 / 1000 persons-year

DAA- : 55 / 1000 persons-year

adjusted HR = 1.41 (95% CI: 0.79, 2.52);
p = 0.25
with IPTW



No impact of DAA on the risk of HCC recurrence post-liver transplantation for HCV-related HCC

Work in progress. Pol S, Mouliade C, Lam L, Carrat F. 2025

Conclusion (1)

1. DAAs decrease the risk of HCC occurrence
2. DAAs do not increase the progression of HCC
3. DAAs decrease the risk of HCC relapse
4. DAAs improves the survival of HCV-related HCC
5. DAAs do not impair the access to liver Tx
6. DAAs do not increase the risk of HCC relapse after liver transplantation

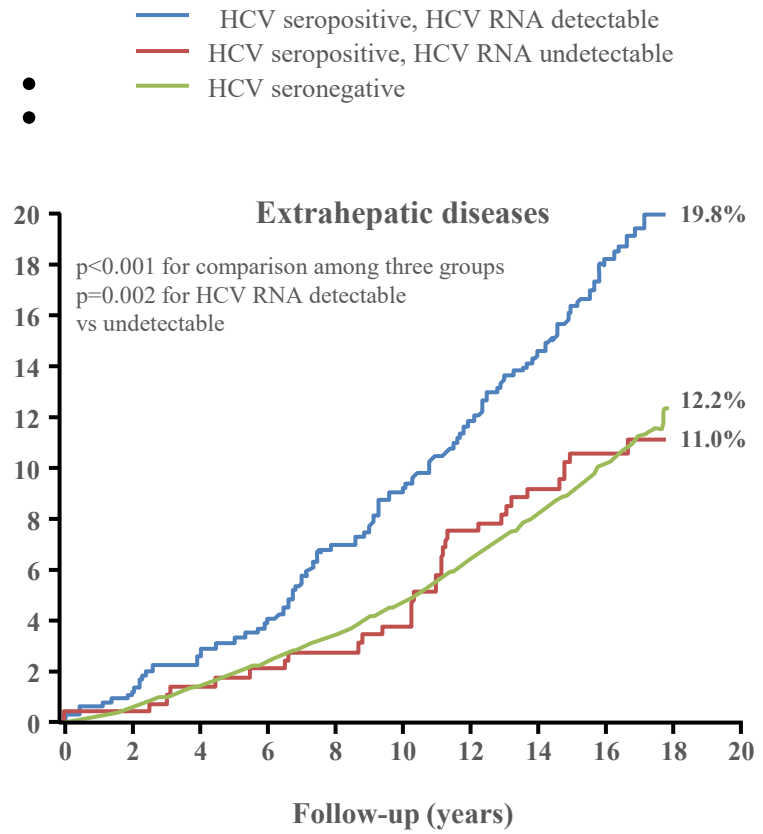
Benefits associated with SVR

- Community benefits associated with SVR : reduction of the contagiosity

- Individual benefits associated with SVR :

  - Hepatic

  - Extrahepatic
    - Vasculitis
    - Chronic inflammation



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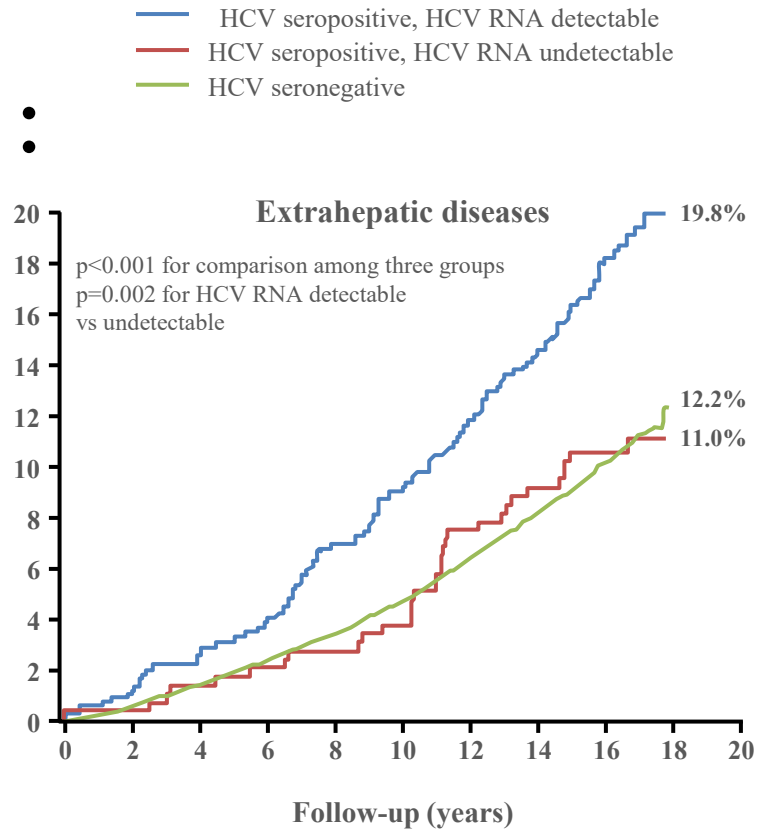
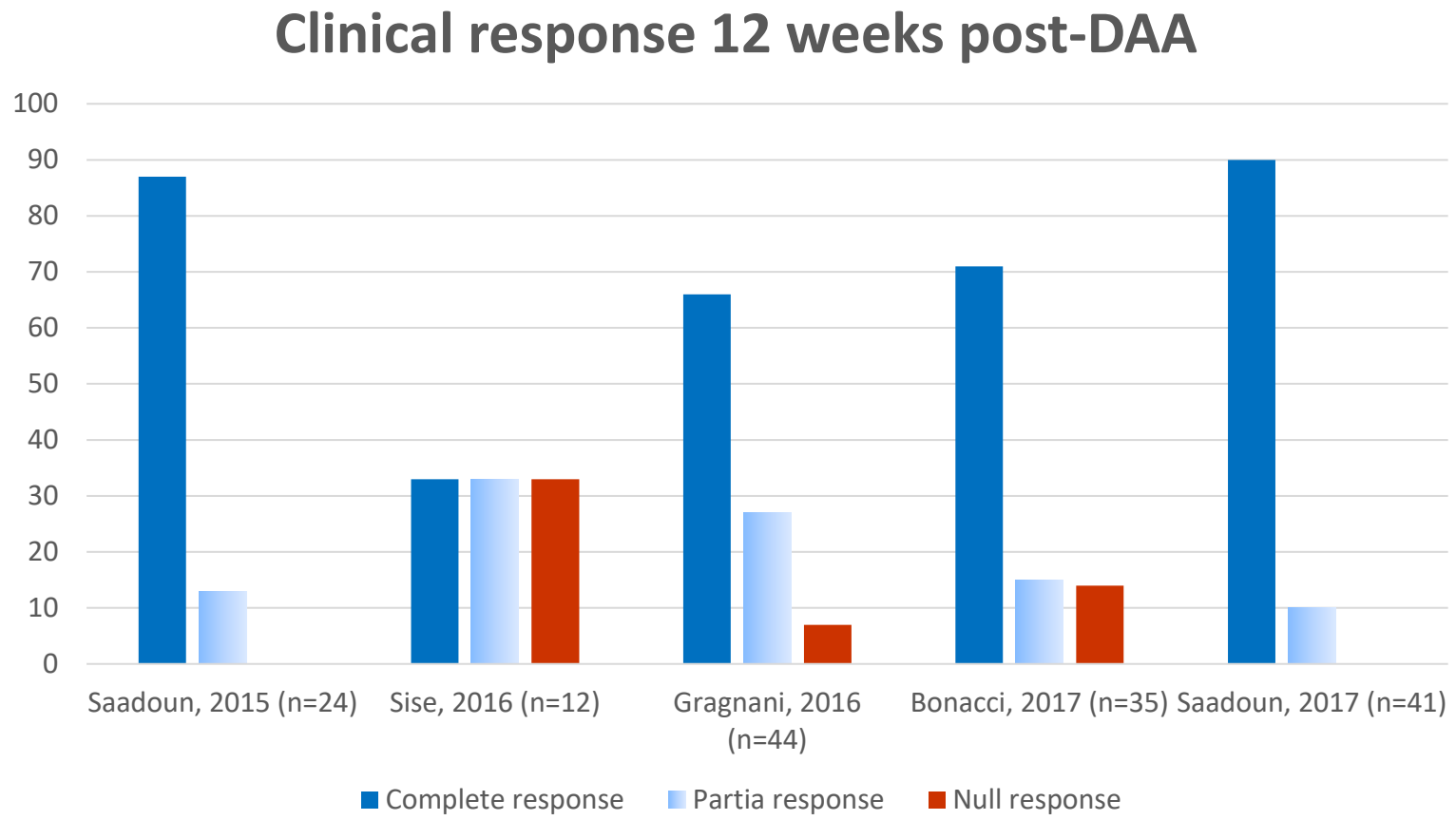


Impact of SVR on vasculitis

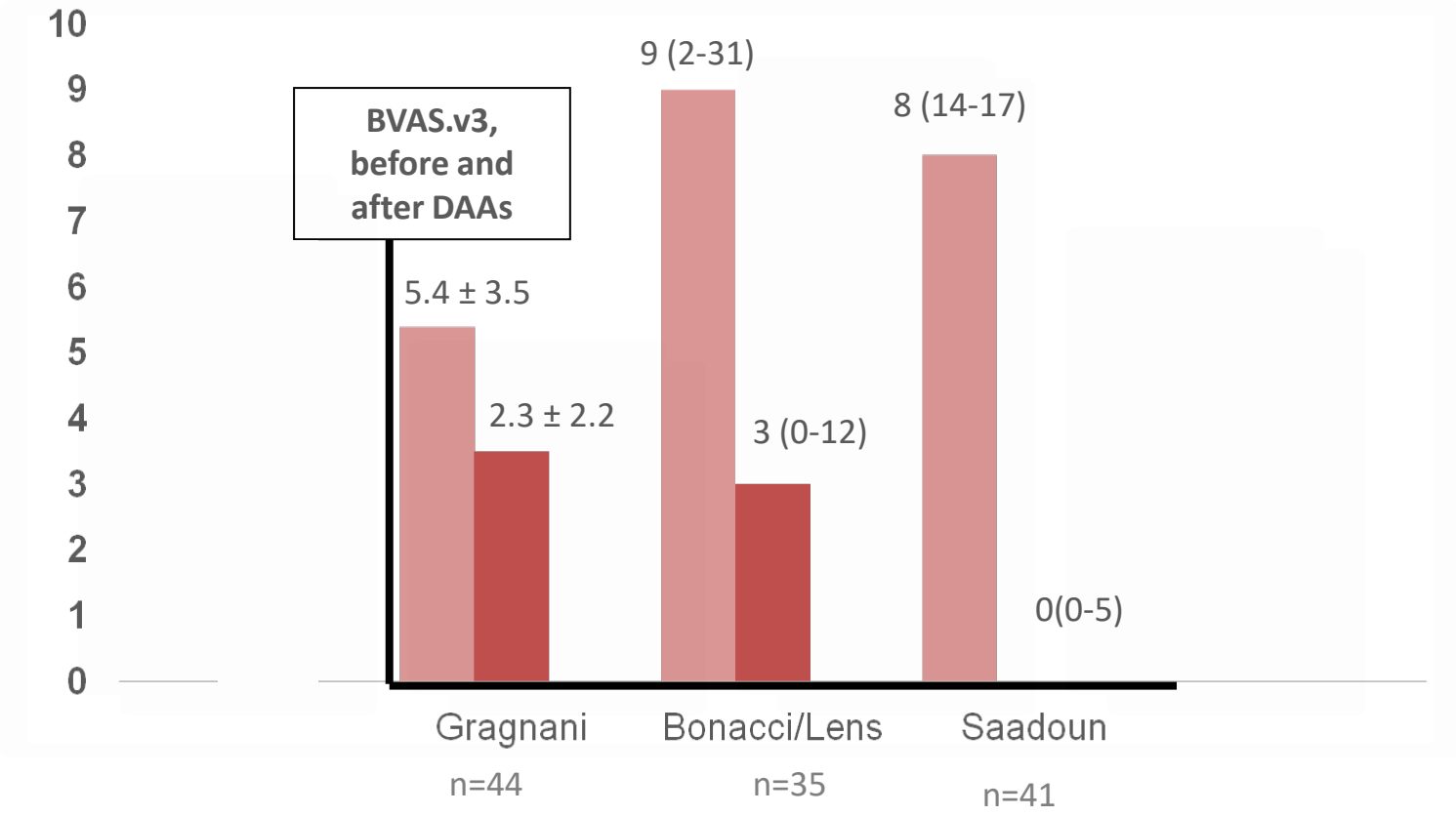
HCV-CryoVas : Impact of DAAs on Clinical Manifestations



Saadoun et al. Ann Rheum Dis. 2016 Oct;75(10):1777-82; Sise et al. Hepatology 2016 Feb;63(2):408-17; Gragnani et al. Hepatology. 2016 Nov;64(5):1473-1482; Bonacci and Lens et al. Clin Gastroenterol Hepatol. 2017 Apr;15(4):575-583. Saadoun et al. Gastroenterology. 2017

Impact of SVR on vasculitis activity

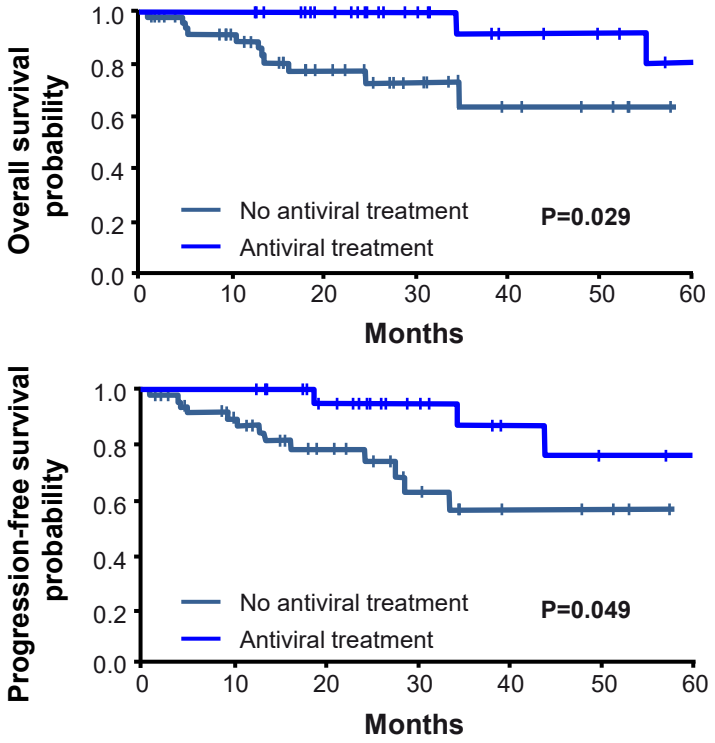
HCV-CryoVas : Less Vasculitis Activity after Direct Antiviral Agents



Gragnani et al. Hepatology. 2016 ;
Bonacci al. Clin Gastroenterol Hepatol. 2017;
Saadoun et al. Gastroenterology. 2017

Sustained Response to IFN-based Antivirals is Associated with Improvements in HCV-related B-Cell Lymphoma

- 116 patients with B-cell lymphoma (DLBCL, 39%; MZL, 39%; other, 22%)
- HCV therapy given to 70 patients
- SVR in 43/70 (61%) patients
  - **SVR correlated with haematological response in MZL (P<0.001)**



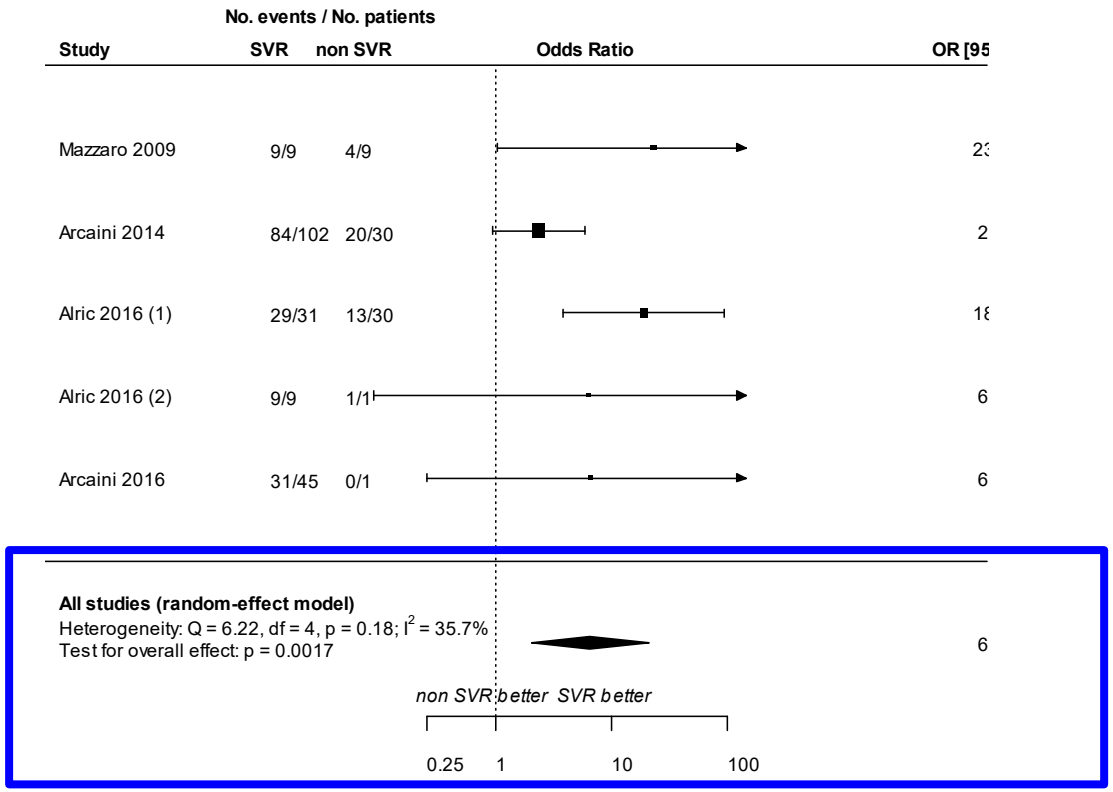
Antiviral therapy was the only variable significantly associated with improved OS (HR:0.18 [0.04–0.95]).

DLBCL: diffuse **large B-cell lymphoma;**
MZL: marginal zone lymphoma;
SVR: Sustained Virological Response

Michot JM, et al. Am J Hematol 2015;90:197–203

Impact of SVR on HCV-related lymphoproliferative disease, a meta-analysis

Outcome: objective hematological response (PR + CR)



Cacoub P et al, Gut 2018

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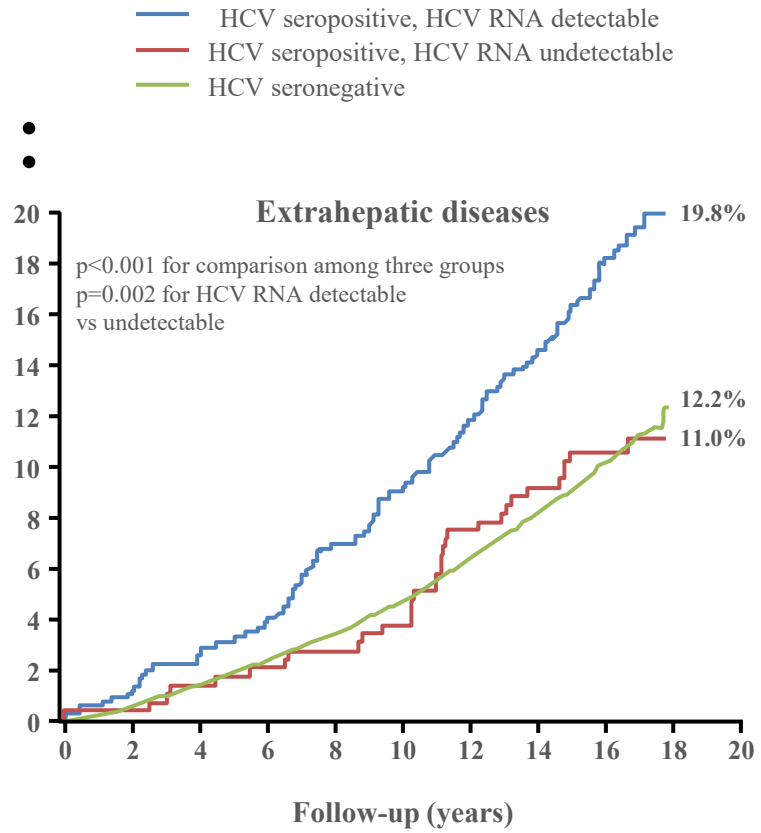
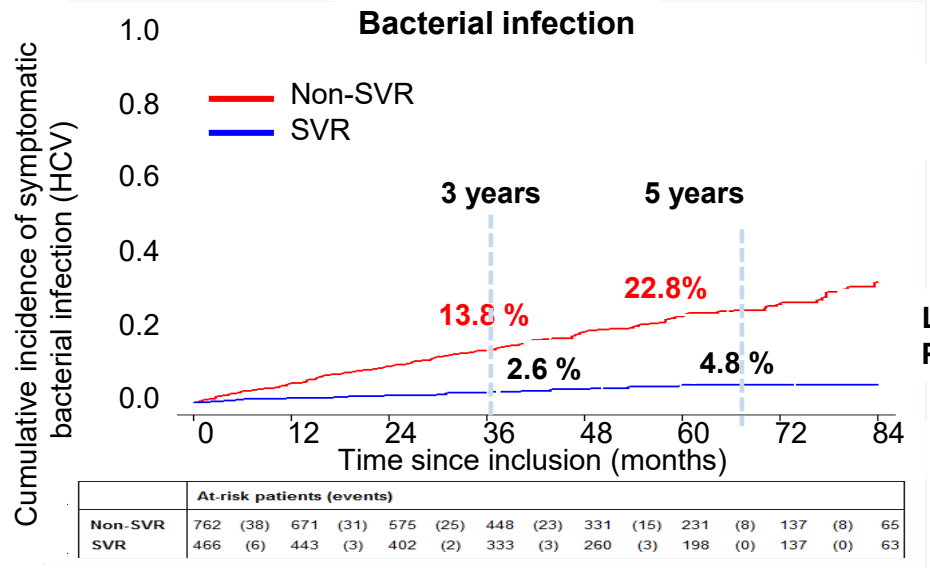
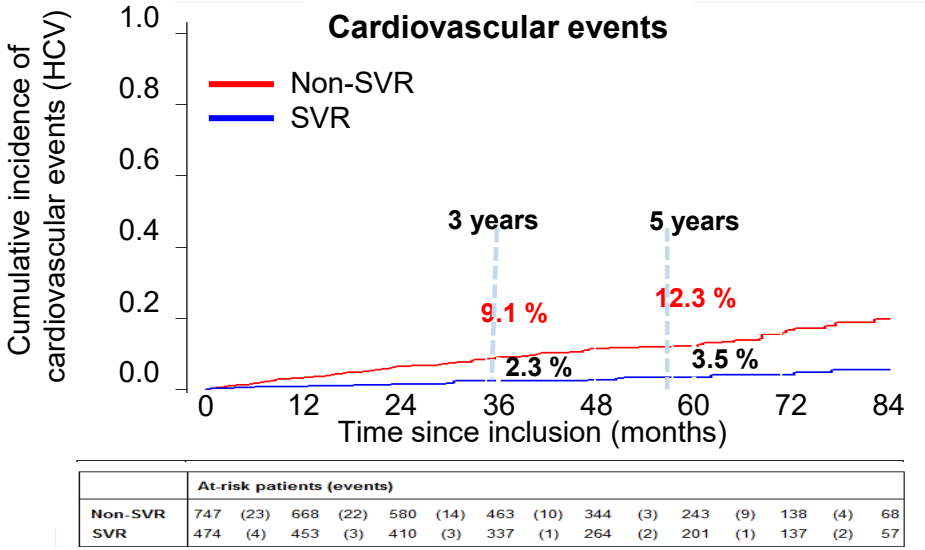


Benefits associated with SVR in cirrhotics

CO20 CIRVIR



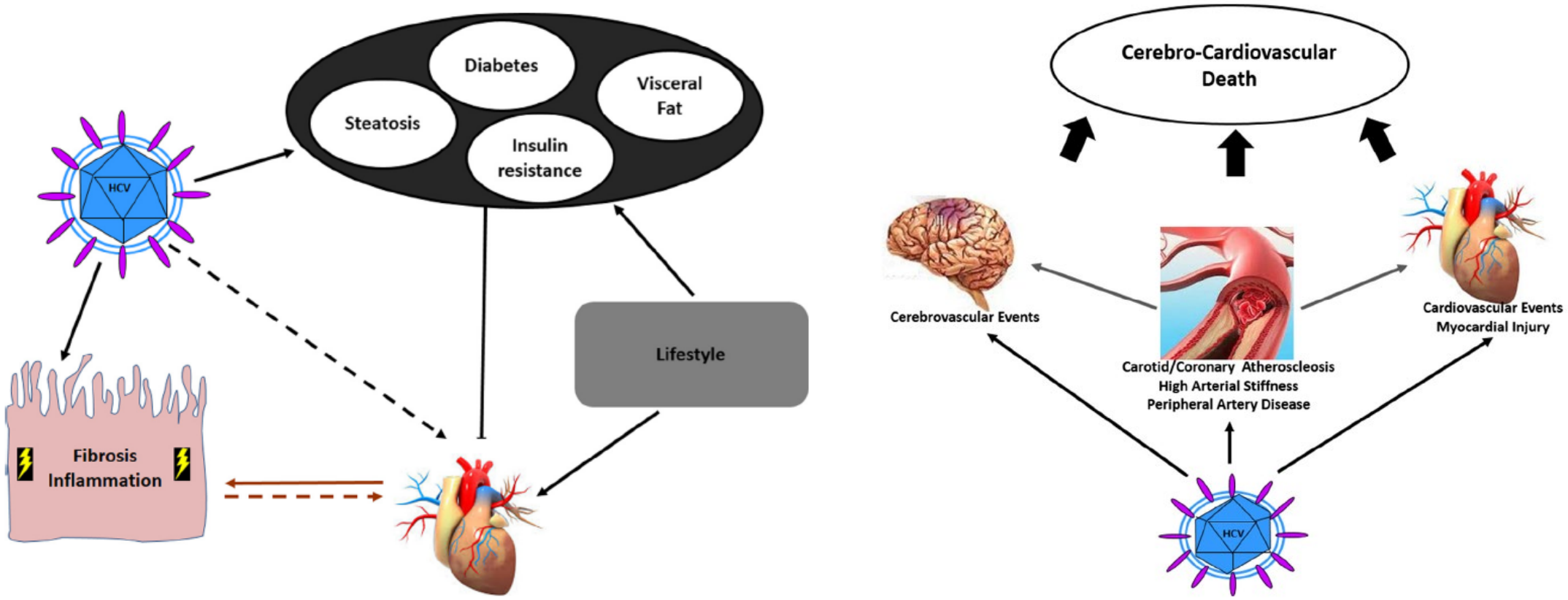
Log-rank P<0.0001



Log-rank P<0.0001

Nahon P et al. Gastroenterology 2017

Extra-hepatic benefits associated with SVR



- Excess risk of cardiovascular mortality [OR 1.65 (95% CI 1.07 to 2.56)]
- Carotid plaques [OR 2.27 (1.76 to 2.94)]
- Ischemic stroke in HCV patients treated vs. untreated (1.2% vs. 1.8%; p <0.001), the risk reduction estimated between 38 and 61% after adjustment for known risk factors.

Petta S. J Adv Res 2020

CO22
HEPATHER

Reduction of cardio-vascular risks in fibrotic patients (n = 3586)

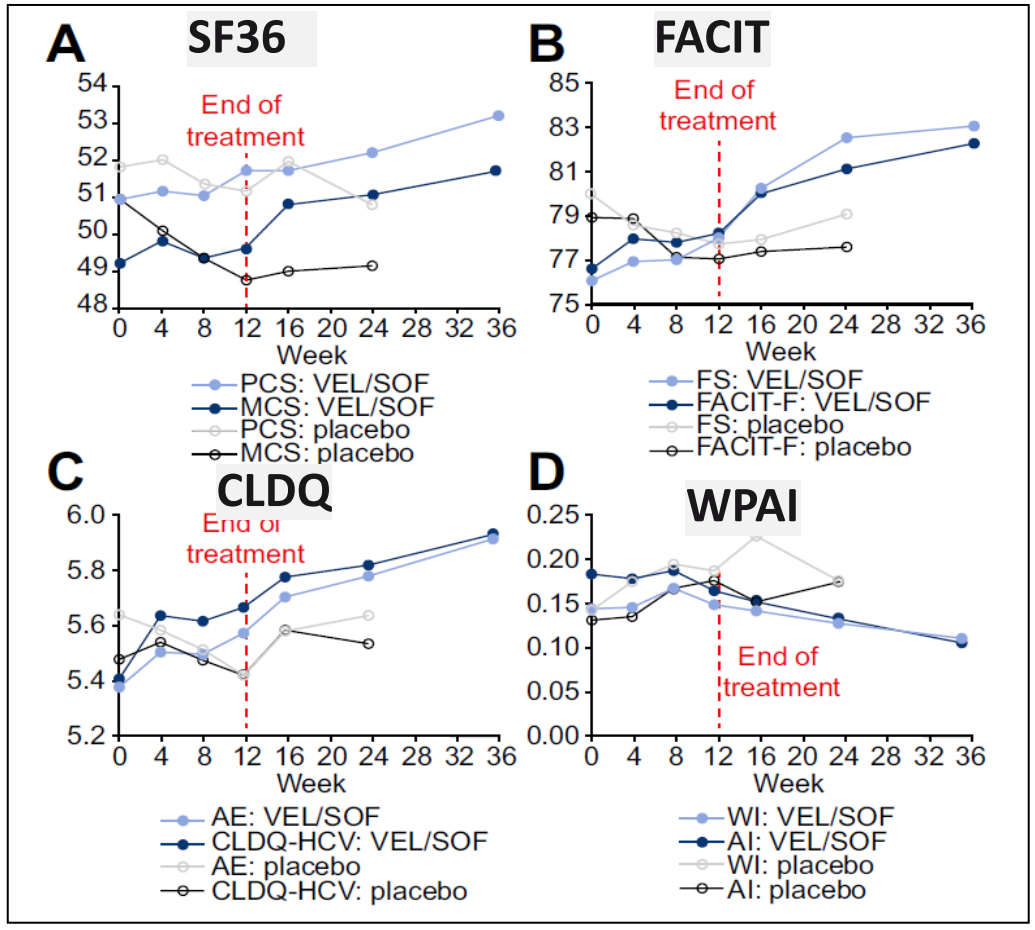
Outcomes	Adjusted hazard ratios associated with DAAs (95% Confidence Interval)
Acute stroke	0.58 (0.29, 1.18)
Acute coronary syndrome	0.59 (0.29, 1.19)
Acute pulmonary embolism	0.79 (0.16, 3.97)
Acute heart failure	0.47 (0.27, 0.81)
Arrhythmias and conduction disorders	1.02 (0.57, 1.84)
Peripheral arterial disease	0.36 (0.17, 0.73)
Major cardiovascular events	0.50 (0.36, 0.71)
Any cardiovascular events	0.58 (0.42, 0.79)
Any extrahepatic solid cancer[c]	0.39 (0.09, 1.71)

Lam L et al. 2022

Extra-hepatic benefits associated with SVR

Patients Reported Outcomes (PROs) at Week 24 after antiviral therapy or placebo

- **PLACEBO**
- **SOF/VEL**

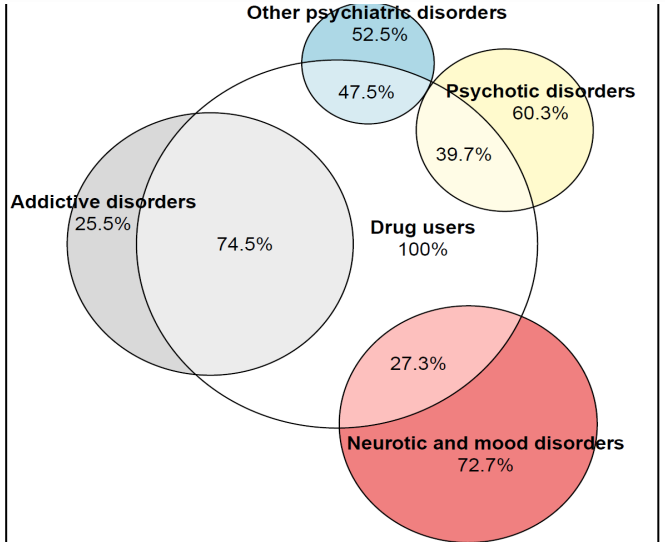


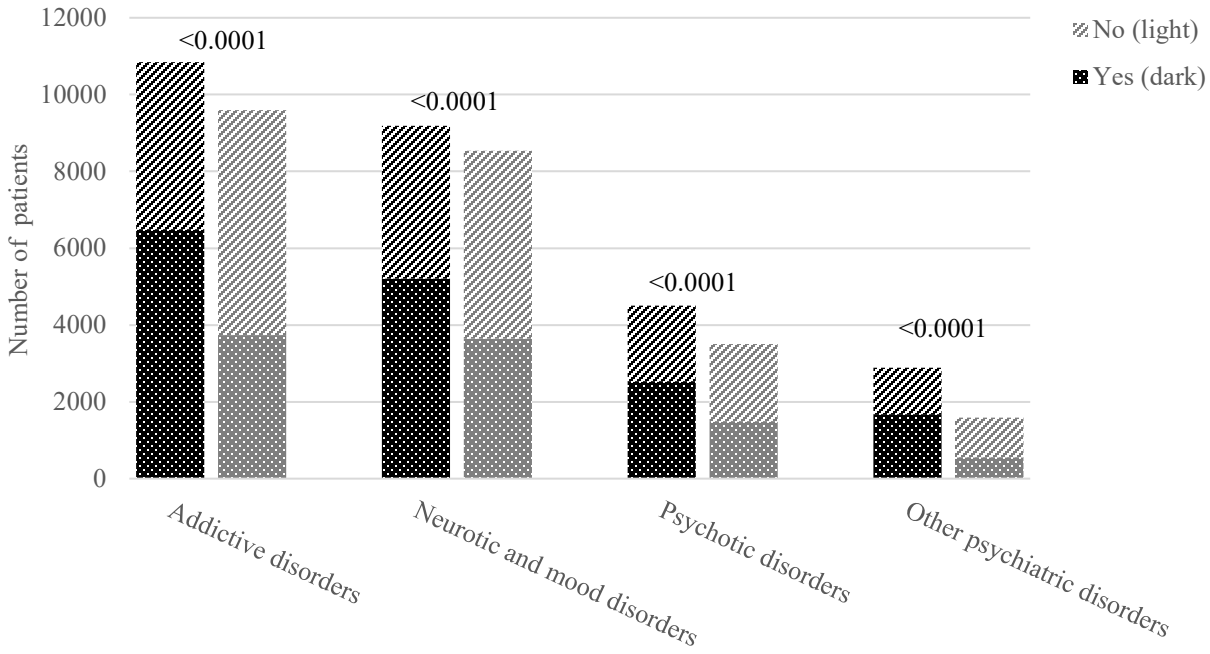
Younossi Z et al, J Hepatol 2016

Extra-hepatic benefits associated with SVR:
BaroC-Psy

Table 1: Patient characteristics of HCV treated patients with psychiatric disorders

	Addictive disorders (N=10,218)	Neurotic and mood disorders (N=8,864)	Psychotic disorders (N=4,004)	Other psychiatric disorders (N=2,239)	Total (N=17,203)
Gender, % (n)					
Male	7,949 (77.8)	4,565 (51.5)	2,617 (65.4)	1,435 (64.1)	11,109 (64.6)
Female	2,269 (22.2)	4,299 (48.5)	1,387 (34.6)	804 (35.9)	6,094 (35.4)
Age,					
Median (range)	50.0 (19-86)	54.0 (18-93)	52.0 (19-88)	51.0 (19-101)	52.0 (18-101)
Q1-Q3	[45.0-55.0]	[49.0-61.0]	[46.0-57.0]	[46.0-57.0]	[47.0-58.0]
Age per class, % (n)					
18≤age<35	5.9 (606)	3.0 (267)	4.5 (179)	4.9 (110)	4.5 (766)
35≤age<45	18.4 (1,882)	10.3 (911)	16.6 (665)	16.3 (366)	14.0 (2,412)
45≤age<55	49.9 (5,102)	37.1 (3,286)	44.4 (1,779)	44.8 (1,004)	42.2 (7,262)
55≤age<65	22.6 (2,314)	30.5 (2,707)	26.5 (1,062)	24.6 (551)	27.2 (4,676)
65≤age<75	2.6 (267)	11.6 (1,024)	6.1 (244)	6.1 (136)	7.7 (1,327)
age≥75	0.5 (47)	7.5 (669)	1.9 (72)	3.2 (103)	4.4 (760)





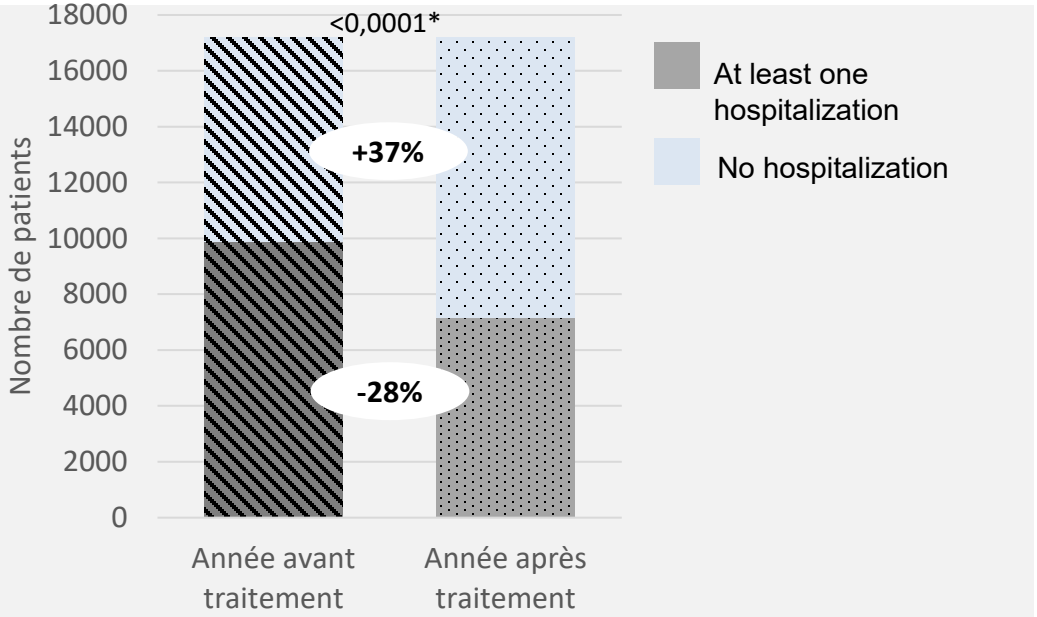
BaroCPsy study. Rolland B et al. Psychiatry Research 2024

Extra-hepatic benefits associated with SVR:

BaroC-Psy

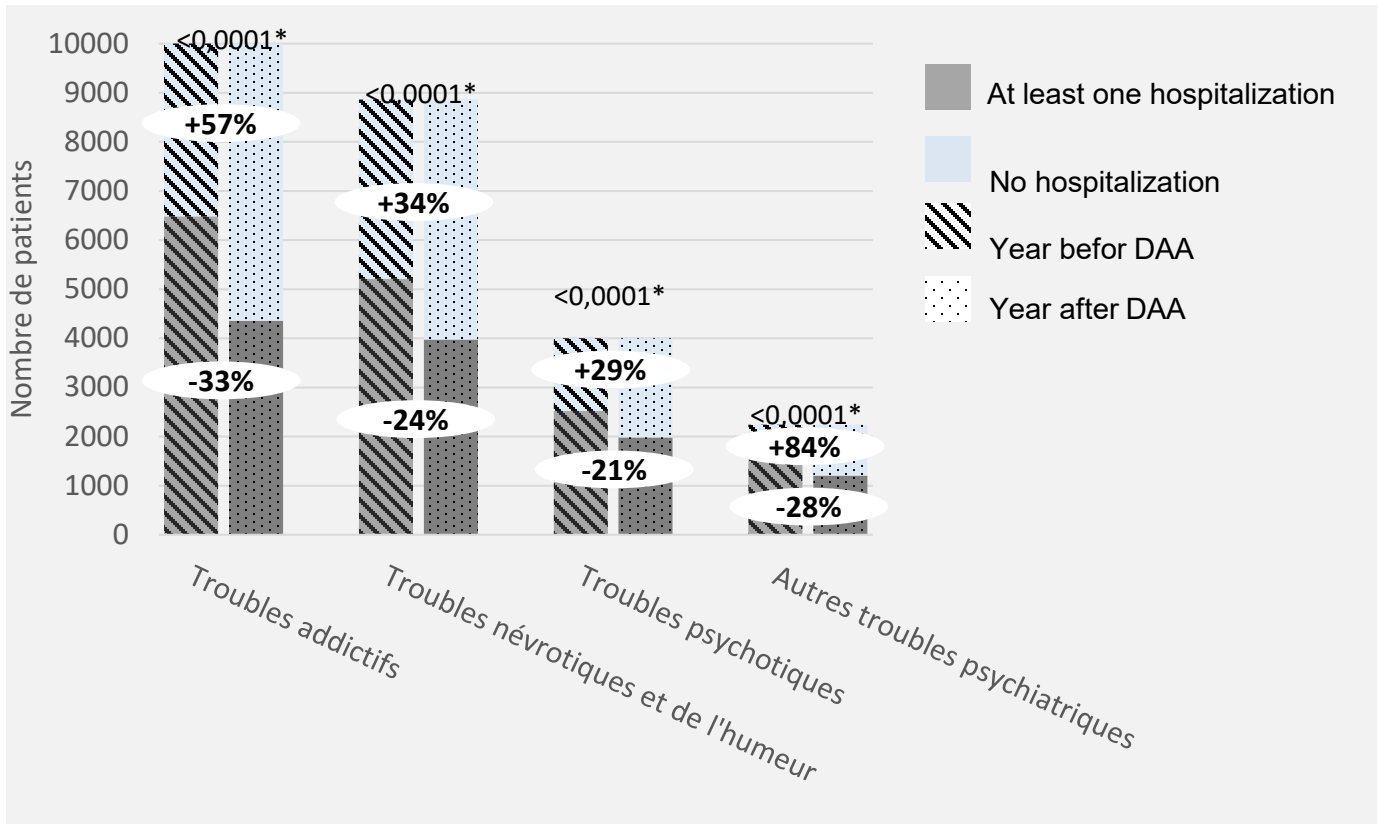
17 203 patients with psychiatric disorders (DAAs between 2015 and 2018 in France)

Overall psychiatric population



*Test de McNemar (P value)

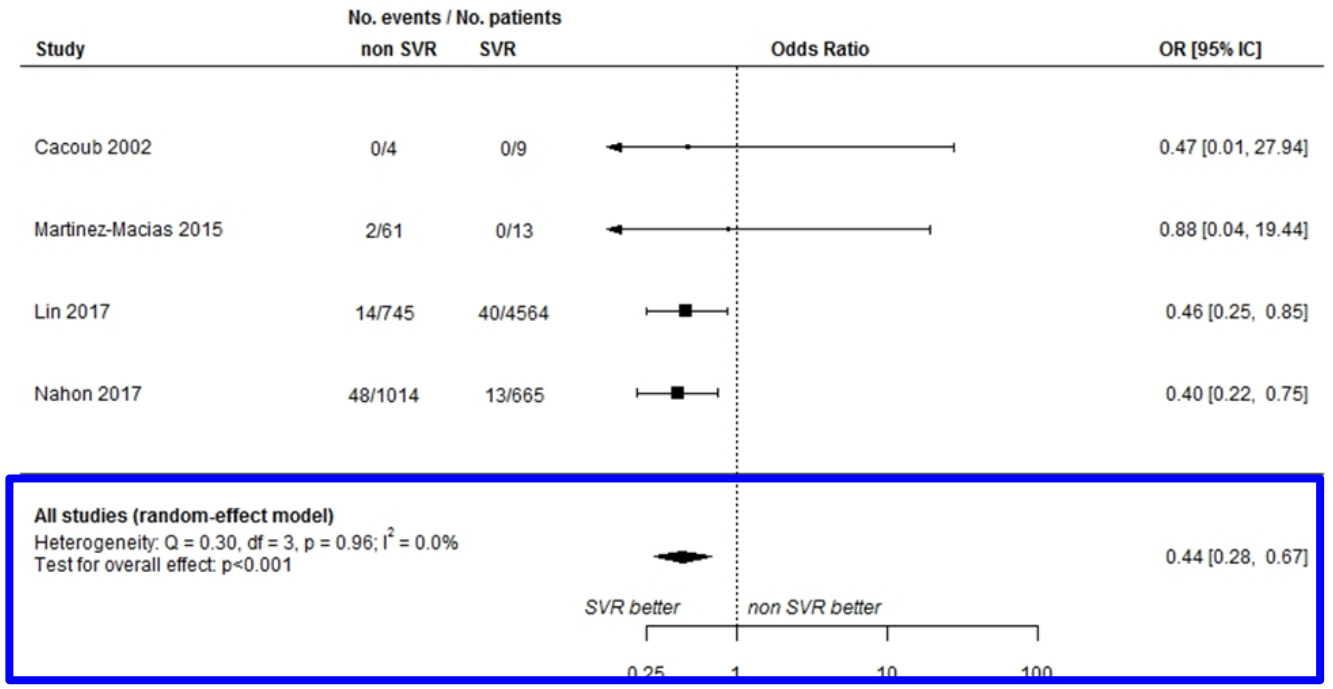
Psychiatric sub-groups



Rolland B. e al. Psychiatry research 2024

Impact of SVR on extra-hepatic mortality in HCV patients, a meta-analysis

Outcome: incidence of extra-hepatic death

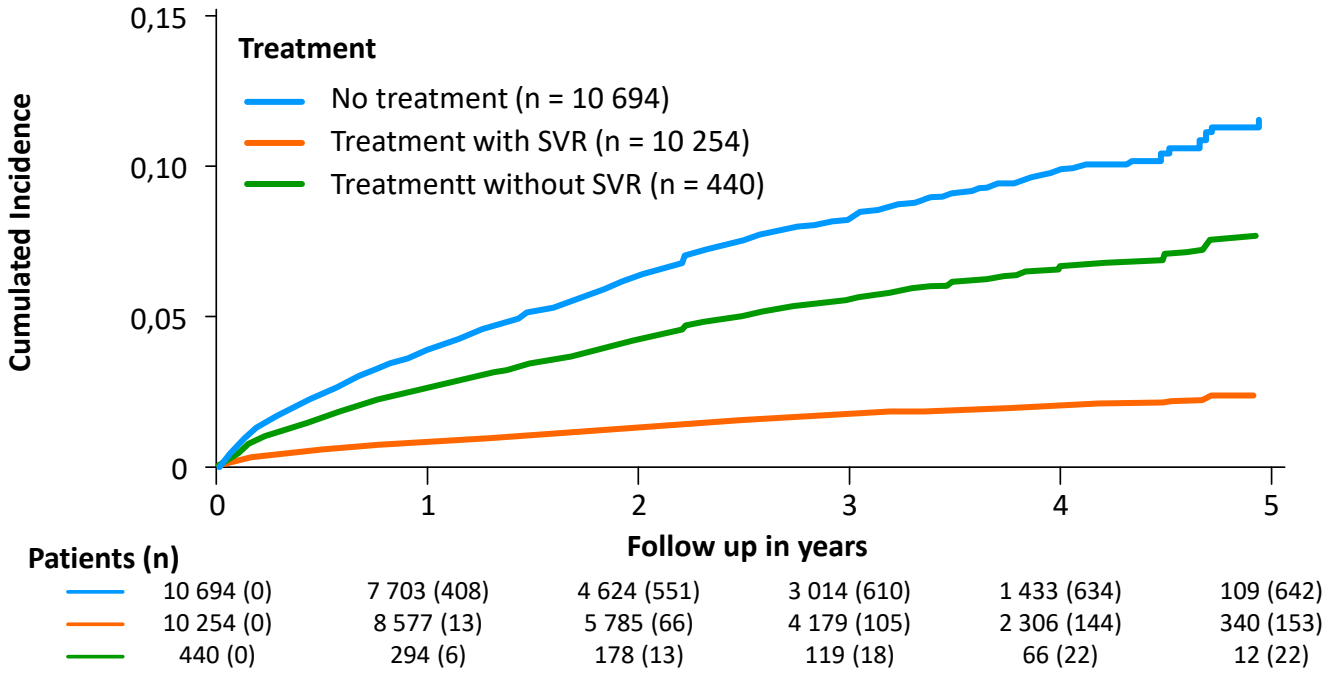


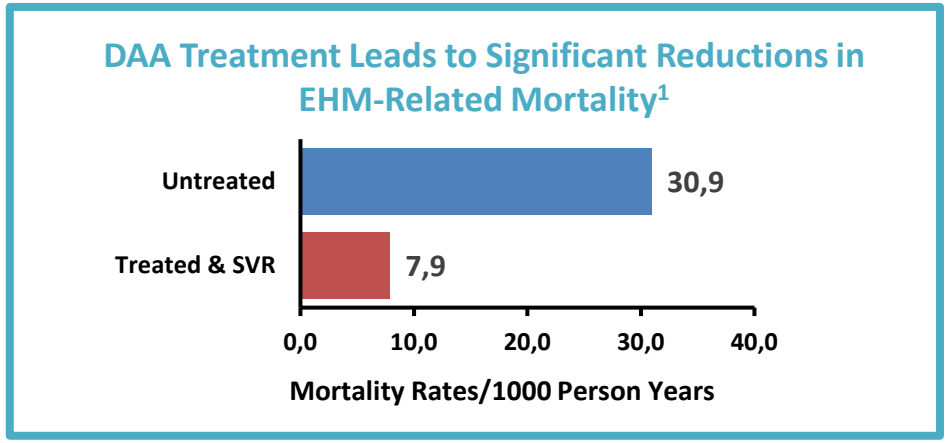
Cacoub P et al, Gut 2018

Extra-hepatic benefits associated with SVR

Cohort study in Canada with a follow-up of 2 to 2.5 years

Mortality associated with extra-hepatic manifestations (EHM)





Treatment with SVR	5.9 (IC 95 % : 5.0-6.9)
Treatment without SVR	25.3 (IC 95 % : 16.7-38.5)
No treatment	29.4 (IC 95 % : 27.2-31.8)

DAAs are associated with a 84% reduction of EHM mortality but the risk persists in patients with comorbidities

Jeong D, *et al. Lancet Reg Health* 2024; **29:**100658

Conclusions (2)

- The DAAs treatment should be proposed to any HCV-infected patient

- At the acute phase for individual and community (reduction of the reservoir and consequently of infection and re-infection) benefits as well as at the chronic phase (reduction of hepatic and extra-hepatic complications)

Acknowledgments

- Fabrice Carrat
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- Laurent Lam