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Update: HCV e malattia sistemica

Workshop
NOVITA' IN INFETTIVOLOGIA.
AUTUMN 2018.
Bologna, 23 Novembre 2018
Società Medica Chirurgica di Bologna – Palazzo dell'Archiginnasio

Pooled prevalence and odds ratios for some HCV-associated extrahepatic manifestations (EHM)

A meta-analysis (n=102 studies) of prevalence, QOL and economic burden

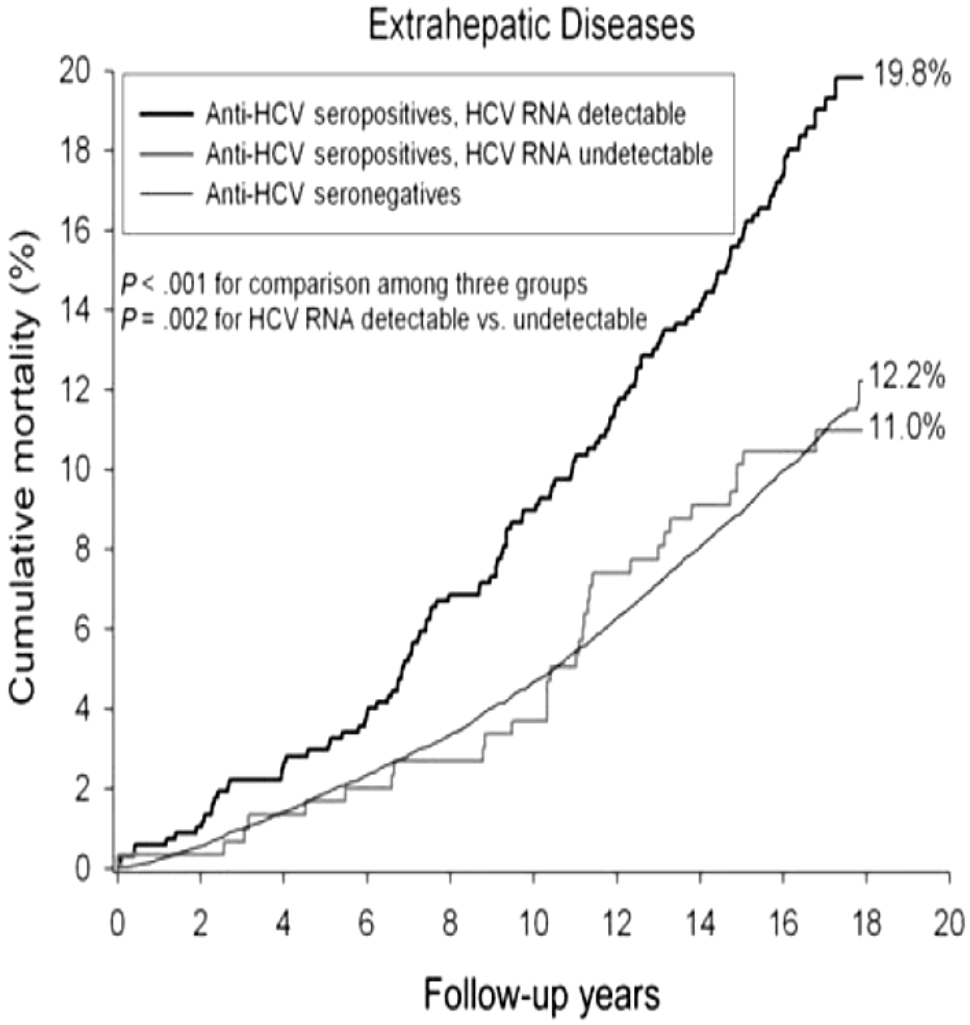
EHM	Prevalence in HCV, % (95% CI)	Prevalence in non-HCV, % (95% CI)	OR (95% CI)	No. of studies included in HCV and non-HCV (sample size)
MC*				
Any MC	30.1 (21.4–38.9)	1.9 (0.4–3.4)	11.50 (4.56–29.00)	21 studies (n = 4145); 7 studies (n = 585)
Symptomatic MC (vasculitis)	4.9	0.0		
CRD (including end-stage)	10.1 (6.7–13.4)	7.6 (4.7–10.5)	RR = 1.23 (1.12–1.34)	14 studies (n = 336,227 HCV; n = 2,665,631 non-HCV)
DM	15 (13–18)	10 (6–15)	1.58 (1.30–1.86)	31 studies (n = 61,843); 19 studies (n = 202,130)
Lymphoma	NA	NA	RR = 1.60 (1.34–1.86)	16 studies**
Lichen planus	1.9 (1.2–2.5)	1.1 (0.3–1.8)	2.27 (1.41–5.66)	18 studies (n = 40,063); 8 studies (n = 138,811)
Sjögren's syndrome	11.9 (7.6–16.2)	0.7 (0.00–3.3)	2.29 (0.19–27.09)	11 studies (n = 38,789); 2 studies (n = 136,845)
PCT	0.5 (0.1–0.8)	0.0 (0.0–0.1)	8.53 (4.15–17.52)	7 studies (n = 970,315); 3 studies (n = 18,763,644)
Rheumatoid arthritis	1.0 (0.0–2.0)	0.09 (0.00–0.09)	2.39 (1.52–3.77)	4 studies (n = 10,970); 1 study (n = 199,568)
Depression	24.5 (14.1–34.9)	17.2 (13.4–21.0)	2.30 (1.31–4.01)	12 studies (n = 139,039); 3 studies (n = 127,506)

***MC, mixed cryoglobulinemia; DM, diabetes mellitus; PCT, porphyria cutanea tarda; CRD, chronic renal disease;**

****Lymphoma studies included 207,284 HCV-infected persons**

YOUNOSSI *et al,* Gastroenterology 2016;150:1599-1608

Mortality from extrahepatic diseases in anti-HCV+, HCV RNA- is comparable to uninfected controls



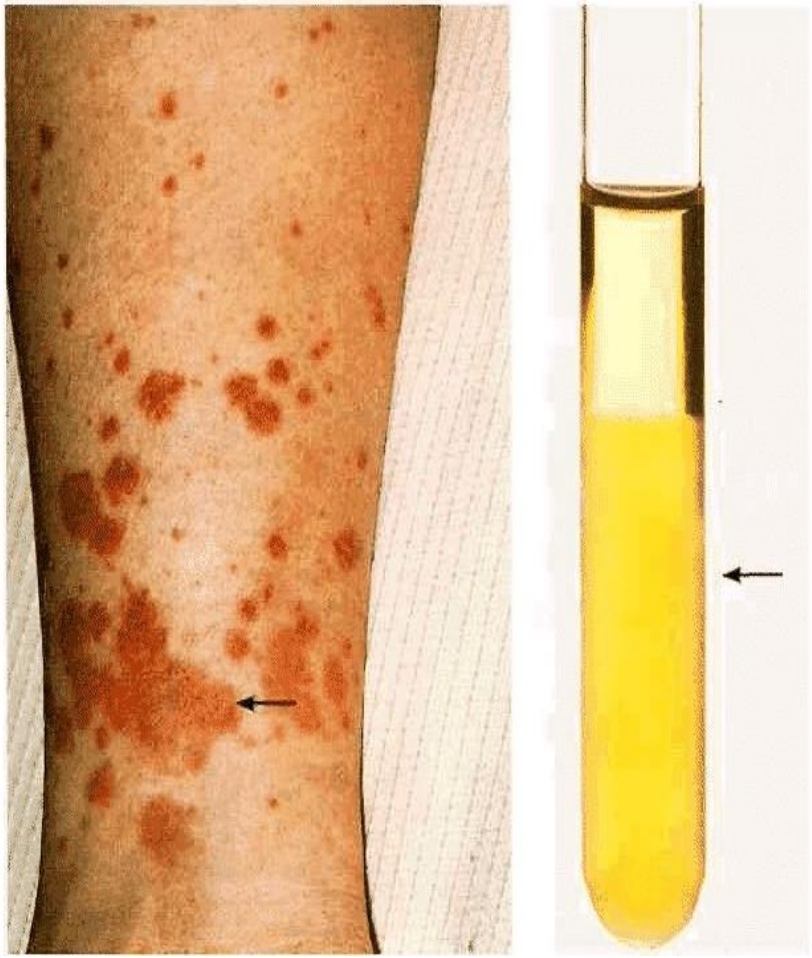
LEE *et al*, J Infect Dis 2012;206:469-77

HCV infection and extrahepatic manifestations: generalities

- Multifaceted pathogenesis
  - Severe liver dysfunction (e.g. porto-systemic encephalopathy)
  - Direct infection of non-hepatocytes (CNS dysfunction)
  - Secretion of substances with endocrine effects (IR)
  - Abnormal immune reactions (autoimmunity, immune complex deposition)
- May or may not respond to antivirals (point-of-no-return)
- May coexist with comorbidities leading to the same or similar clinical picture

Myxed cryoglobulinemia and its consequences

Mixed cryoglobulinemia-associated cutaneous vasculitis, arthralgia and fatigue: on-treatment response to IFN-α, followed by recurrence upon withdrawal



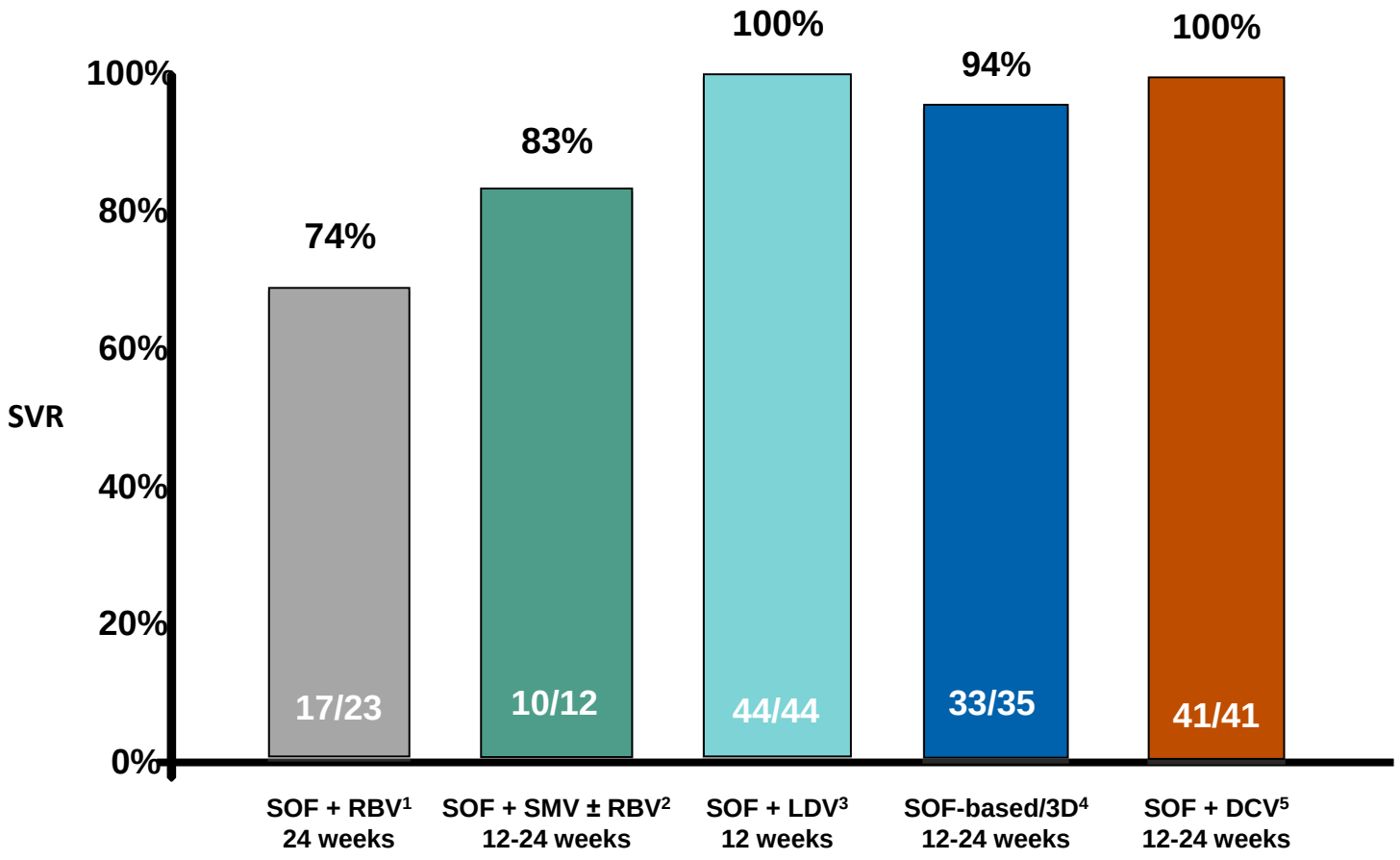
Shakil AO & Di Bisceglie AM. N Engl J Med 1994;331:1624

HCV-related cryoglobulinemia

Vasculitis affecting *vasa nervorum* (epineural arterioles)

Irreversible ischemic nerve damage
(axonal degeneration and loss, demyelination)

Virological Response after IFN-free DAA therapy of HCV-associated CG

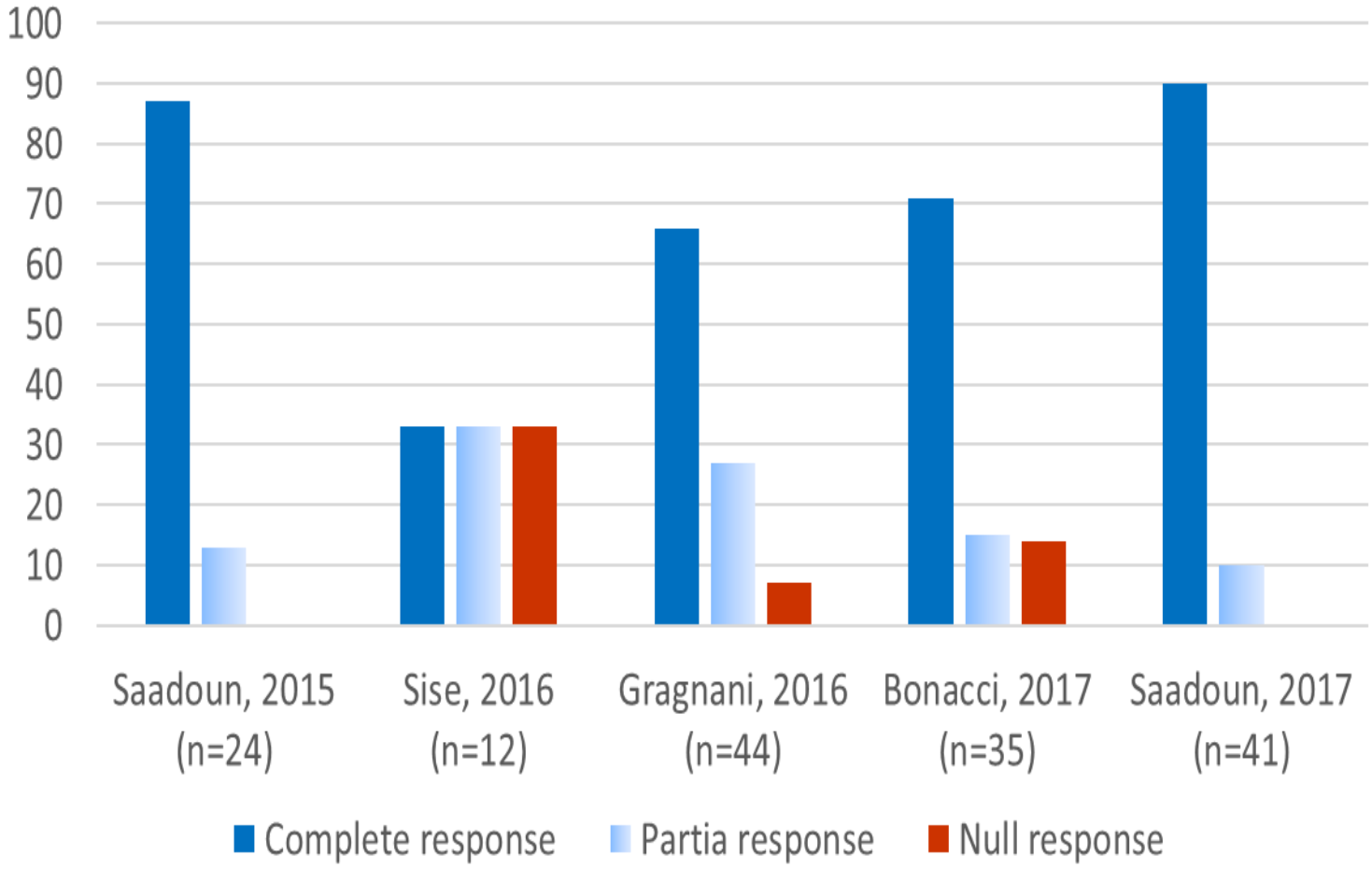


1.SAADOUN *et al,* Ann Rheum Dis 2015; 2. SISE *et al,* Hepatology 2016; 3. GRAGNANI *et al,* Hepatology 2016
4. BONACCI *et al,* Clin Gastro Hepatol 2016 ; 5. SAADOUN *et al,* Gastroenterology 2017

Impact of DAA therapy on CG

Author	Cryocrit before therapy	Cryocrit 12 weeks after therapy	Cryo -
Saadoun *et al*, 2016	0.35 (0.156 – 0.83) g/L	0 (0 – 0.37) g/L	46%
Sise *et al*, 2016	1.5% (0.5 – 4%)	0.5% (0 – 2%)	44%
Gragnani *et al*, 2016	7.2 ± 15%	1.8 ± 5%	39%
Bonacci *et al*, 2017	3.2% (1.5 – 3.7%)	0.5% (0 – 1.4%)	43%
Saadoun *et al*, 2017	0.56 ± 0.18 g/L	0.21 ± 0.14 g/L	50%

Clinical response 12 weeks post-DAA

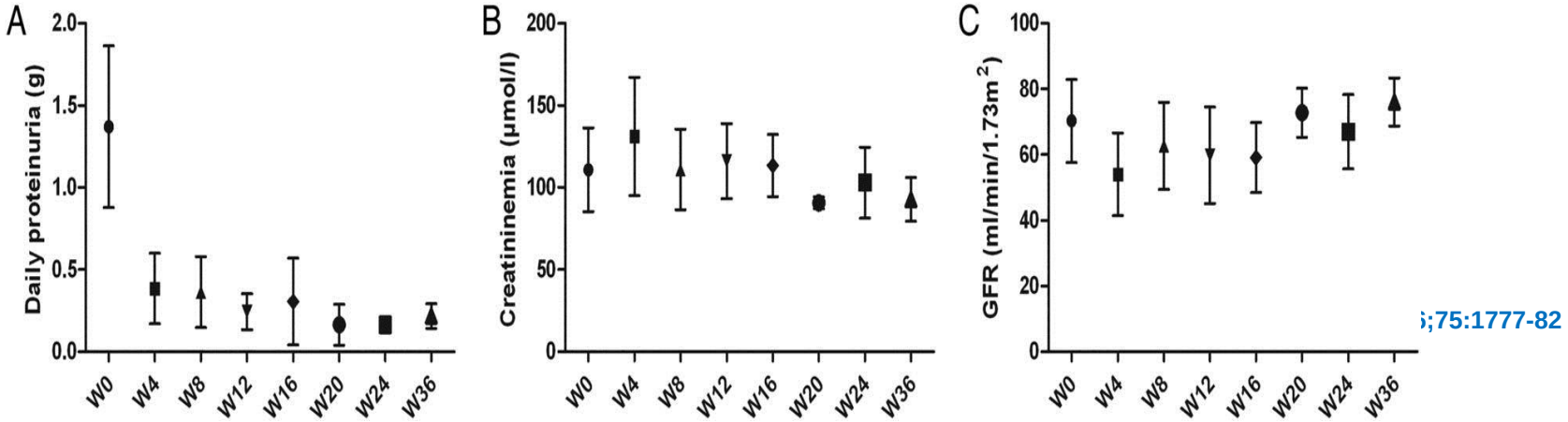


SAADOUN *et al,* Ann Rheum Dis 2015; SISE *et al,* Hepatology 2016; GRAGNANI *et al,* Hepatology 2016
BONACCI *et al,* Clin Gastro Hepatol 2016 ; SAADOUN *et al,* Gastroenterology 2017

DAA for HCV-associated MC-related vasculitis

The VASCUVALDIC Study

- 24 patients with HCV-cryoglobulinemia vasculitis (80% type II, 58% F3 or F4)
- Purpura and peripheral neuropathy (67%), arthralgia (58%), GN (21%), skin ulcers (12%)
- SOF 400 mg QD + RBV (200–1400 mg/d), 24 weeks (7 received immunosuppressants)
- SVR 74%
- Purpura, skin ulcers and arthralgia disappeared in all cases
- Kidney involvement improved in 4/5

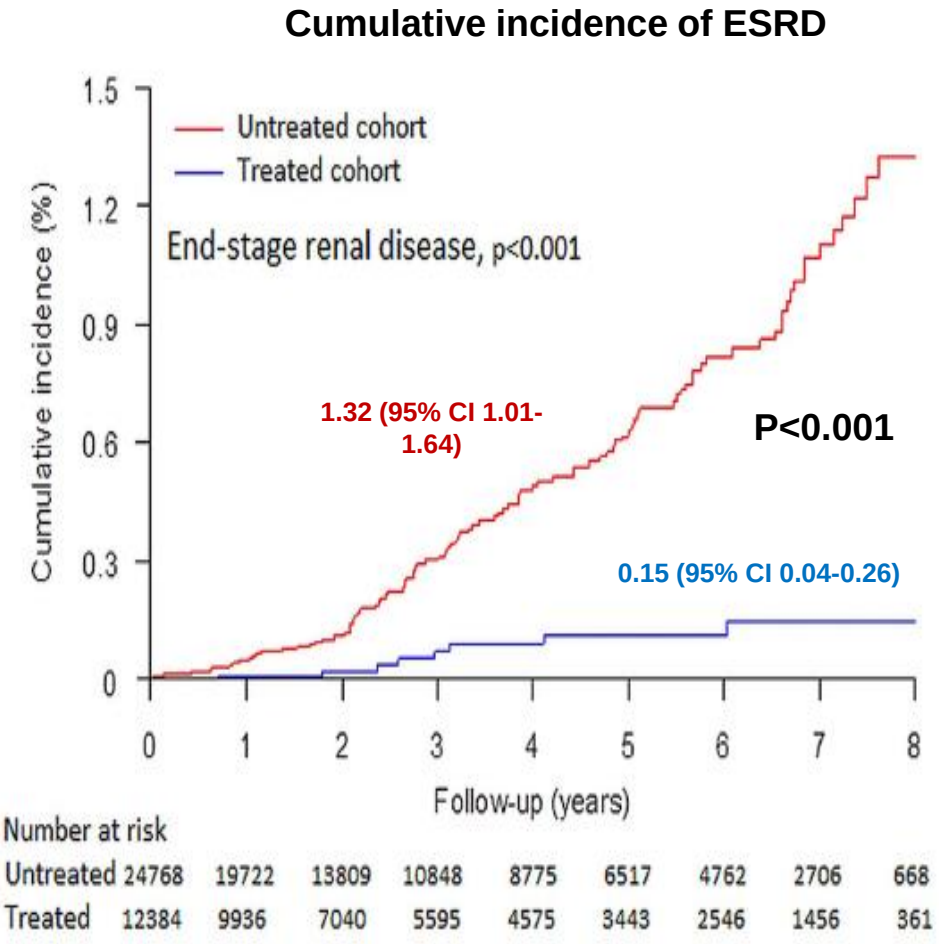


;75:1777-82

Effect of antiviral treatment on renal outcomes

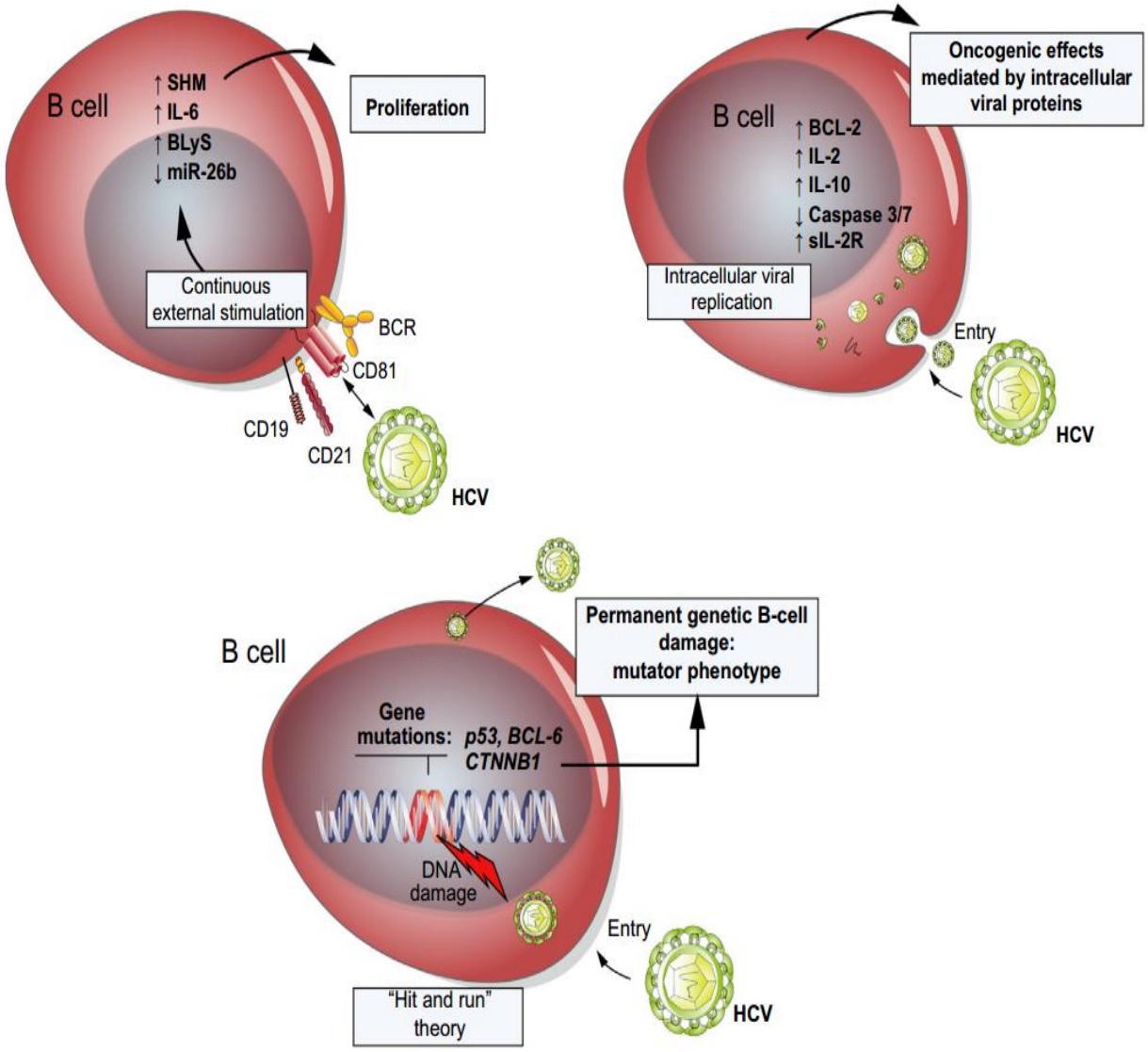
Taiwan National Health Insurance Research Database (NHIRD)

(n=12,384 treated with pegIFN/RBV *vs.* 24,768 untreated controls, matched by propensity scores and length of FU)



HSU *et al*, Gut 2015;64:495-503

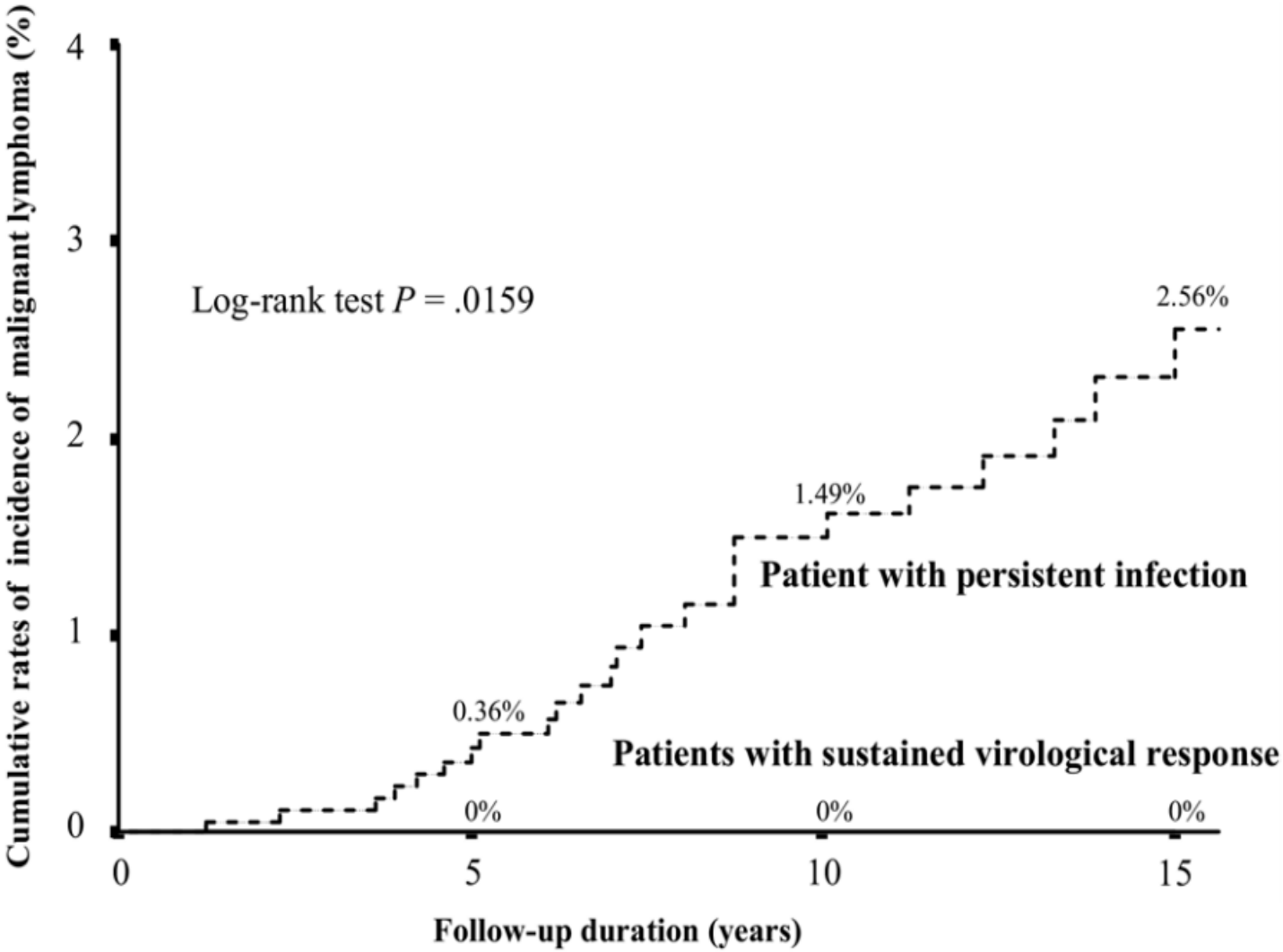
HCV-associated lymphoma: mechanisms



PEVELING-OBERHAG *et al*, J Hepatol 2013;59:169-77

HCV eradication prevents occurrence of lymphoma

Long-term FU of 501 untreated and 2,708 treated HCV patients



KAWAMURA *et al*, Am J Med 2007;120:1034-41

DAA and low-grade non-Hodgkin lymphoma

	Year	No. of patients	Diagnosis	Genotypes	Cryoglobulinemia	Antiviral treatment	Virologic response	NHL response
Rossotti *et al*[58]	2015	1	SMZL	1b	Yes (type Ⅱ MC)	FDV + DLV + RBV (16 w)	SVR	PR
Sultanik *et al*[59]	2015	1	MALT MZL (breast, humeral shaft, cervical lymph node)	3a	Yes (type Ⅱ MC)	SOF + RBV (4 w), then SOF + DCV (12 w)	SVR	CR (ongoing at 6 m)
Carrier *et al*[60]	2015	3	1 Leukemic MZL	4	3 (type Ⅱ MC)	SOF - SIM	3 SVR	PR
			1 MALT MZL (kidney)	1b		SOF - SIM + 4 Rtx		CR
			1 SMZL	1b		SOF - DCV		CR
Lim *et al*[61]	2015	1	SMZL	2	No	SOF + RBV (12 w)	SVR	CR (ongoing at 17 m)
Arcaini *et al*[62]	2015	20	9 SMZL	1 (n = 13)	10 (50%)	various	19 SVR	4 CR, 2 PR, 2 SD 1 PD
			1 NMZL (Nodal)	2 (n = 3)		SOF-based regimens		1 CR
			5 MALT MZL	3 (n = 3)				2 CR, 1 PR, 2 PD
			2 Leukemic MZL	4 (n = 1)		(+ 4 Rtx in 1 pts)		1 CR, 1 PR
			2 CLL					2 SD
			1 LPL					1 SD

MERLI *et al*, World J Gastroenterol 2016;22:844

DAA and high-grade non-Hodgkin lymphoma

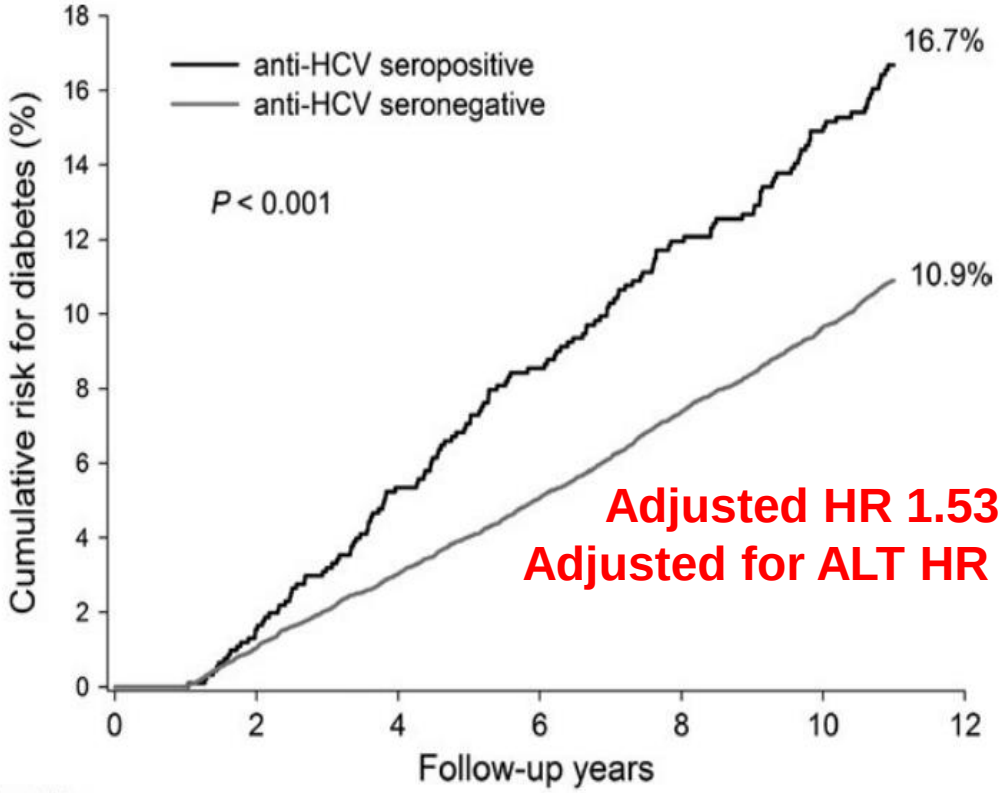
- 20 diffuse large B-cell lymphomas (all HCV-1b) treated with SOF/LDV and chemotherapy vs. historical retrospective cohort of 101 DLBCL/HCV+ patients not receiving antivirals
- At FU (52 weeks), overall survival was similar, but disease-free survival was better among those treated with SOF/LDV (P = 0.036)
- Predictors for improved disease-free survival (by MV): International Prognostic Index and antivirals
- Safety profile: similar

PERSICO *et al*, Hepatology 2018;67:48-55

Insulin resistance and type 2 diabetes

Chronic HCV infection and risk for diabetes: a community-based prospective study

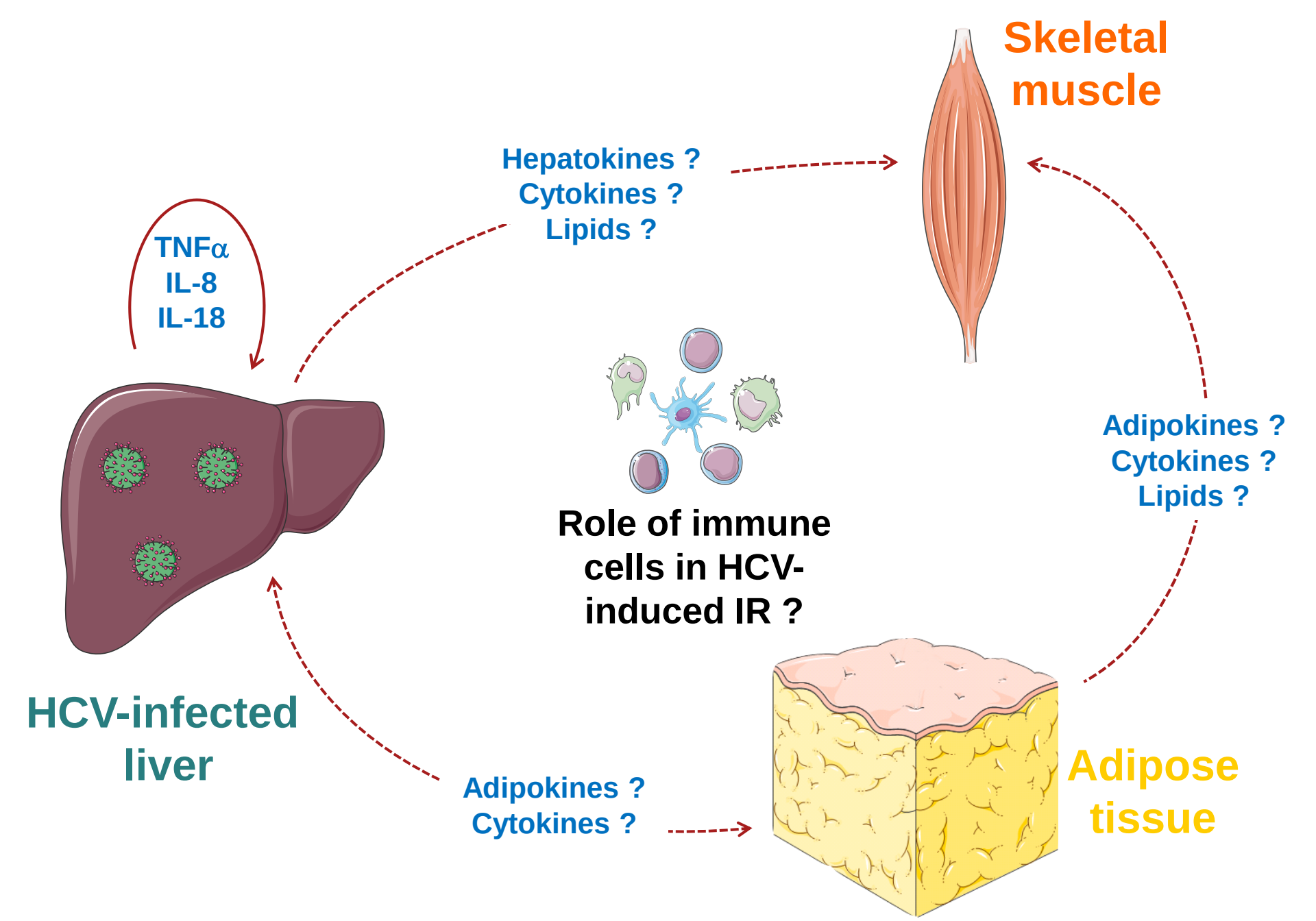
(REVEAL Cohort: n=16,928 anti-HCV- vs. 930 anti-HCV+; 180,244 PY; median FU 11.0 yrs)



Adjusted HR 1.53 (1.29–1.83)
Adjusted for ALT HR 1.40 (1.17–1.67)

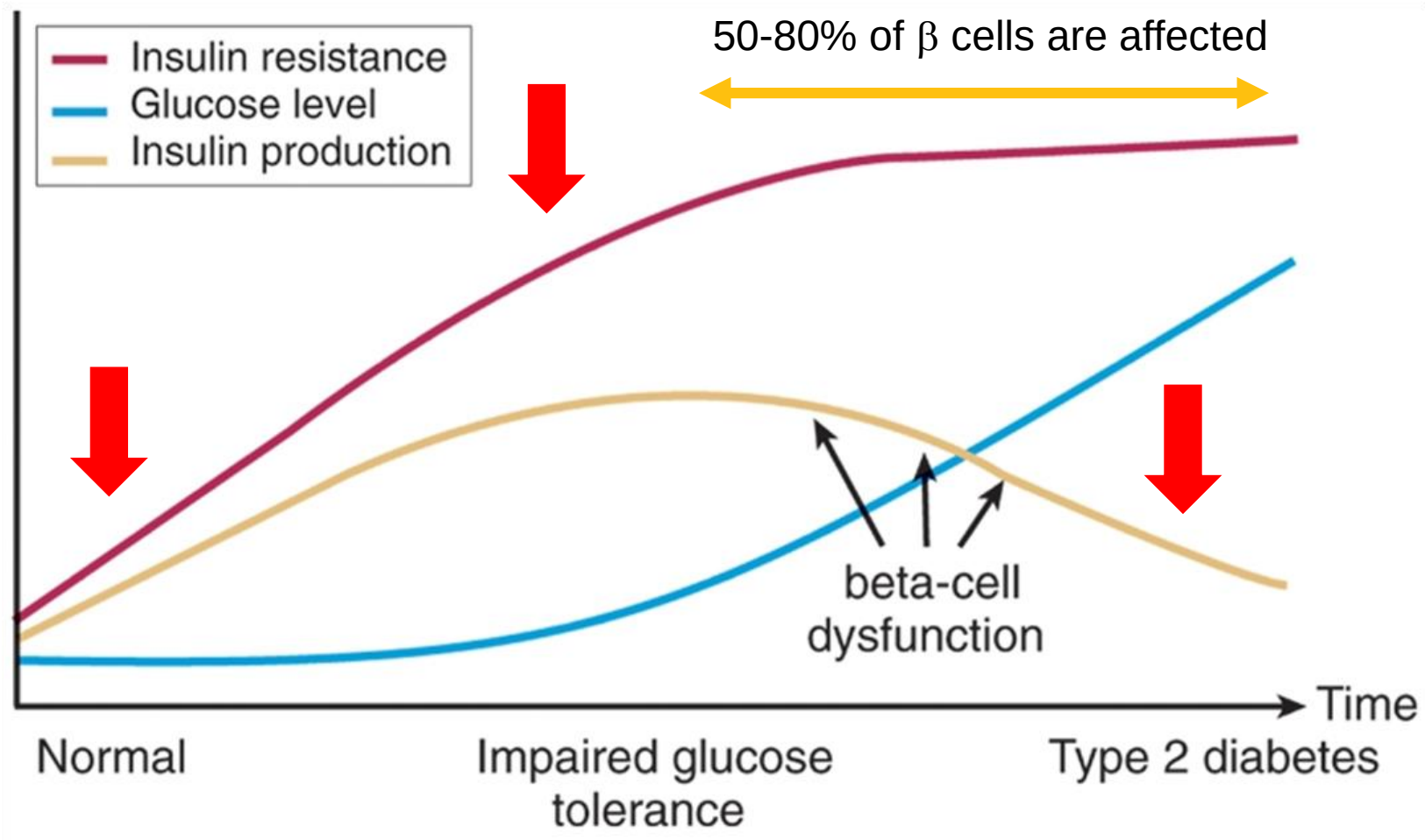
Population at risk						
Anti-HCV seropositives	930	891	834	790	736	679
Anti-HCV seronegatives	16 928	16 575	16 052	15 496	14 888	14 295

LIN *et al,* Liver Int 2016 July 16 [Epub ahead of print]



KADDAI & NEGRO, Exp Rev Gastroenterol Hepatol 2011

From insulin resistance to type 2 diabetes



HENRY, Am J Med 1998;105:20S-26

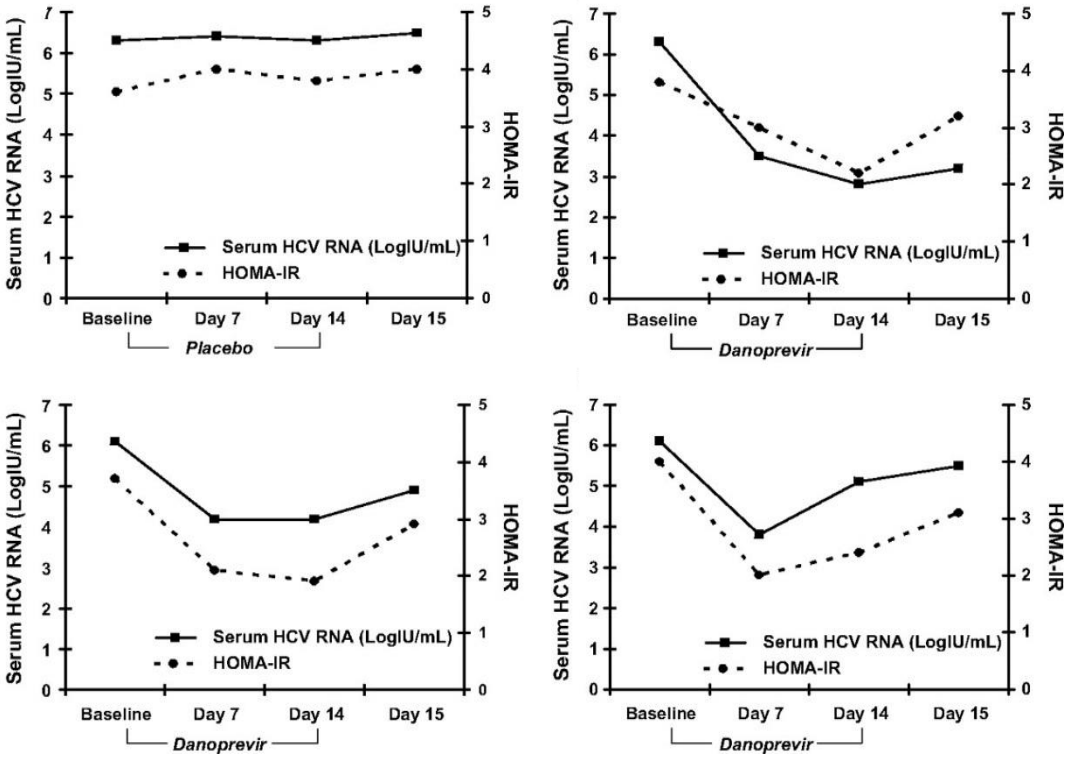
SVR reduces the incidence of insulin resistance during FU

- 431 HCV+ patients (Milan Safety Tolerability Cohort)
- 12% insulin resistant (HOMA-IR>2)
- **After 24 months of FU, *de novo* insulin resistance occurred less frequently in SVR than in non-SVR (7% vs. 17%, p=.007)**

AGHEMO *et al,* Hepatology 2012;56:1681-7

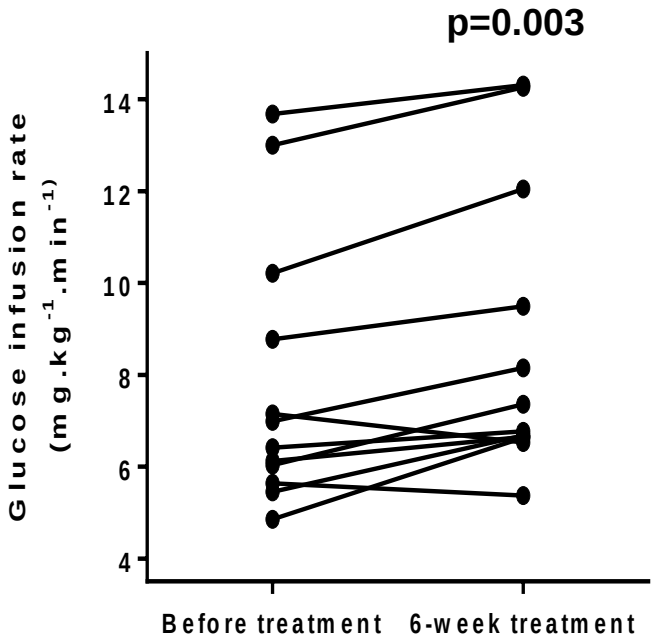
Suppression of serum HCV RNA by IFN-free regimens correlates with improved insulin sensitivity

n = 30, HCV-1, treated with danoprevir



MOUCARI *et al,* Gut 2010;59:1694–1698

n = 12, HCV-3, treated with DAA



GOMES, GASTALDI *et al,* EASD 2017

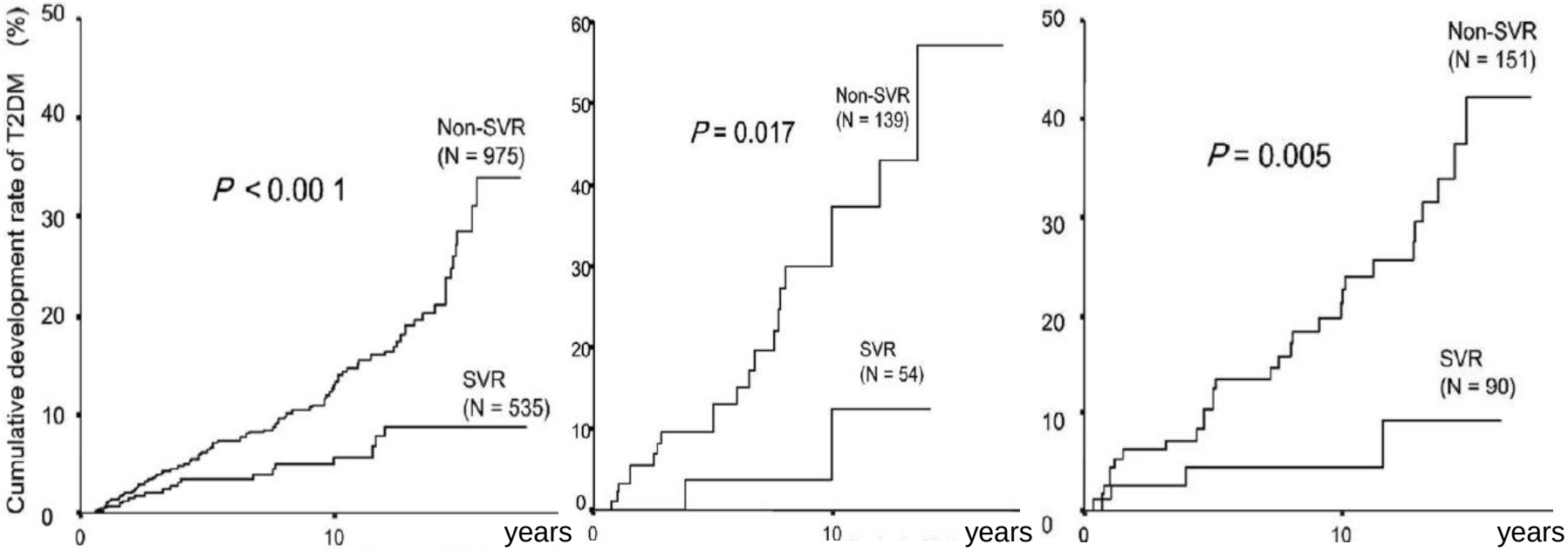
SVR is associated with a two-thirds reduction of the risk of developing diabetes

- 2,842 Japanese non-diabetic patients with chronic hepatitis C
- IFN-α $\pm$ ribavirin
- 143 patients developed diabetes after a 6.4 years: 26/1175 SVR (2.2%) vs 117/1667 non-SVR (7%)

Factor associated with T2D development	HR (95% CI)	p
Advanced fibrosis	3.30 (2.06 – 5.28)	.001
Lack of SVR	2.73 (1.77 – 4.20)	.001
Pre-diabetes	2.19 (1.43 – 3.37)	.001
Age ≥50 years	2.10 (1.38 – 3.18)	.001

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

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



Age >50 years **Cirrhosis** **Pre-diabetes**

Curing HCV reduces the risk of developing diabetes by ~2/3

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

Glycemic Control by DAA in Patients with HCV-4 and Type 2 Diabetes

Variable	IGC group (n=292)		NIGC group (n=86)		Control group (n=60)	
	Before DAAs therapy	3 Months after therapy	Before DAAs therapy	3 Months after therapy	Baseline	After 3 months
FPG, mg/dL						
Range	105–252	85–186	108–248	110–249	108–245	107–248
Mean±SD	184.5±27.9	136.5±22.5	179.9±25.6	181.2±25.9	178.1±24.3	180.1±26.2
HbA1c, %						
Range	6.9–8.7	6.4–7.7	6.8–8.8	6.8–8.7	6.9–8.8	6.8–8.9
Mean±SD	8.1±0.44	7.3±0.34	8.2±0.48	8.1±0.46	8.2±0.43	8.3±0.46

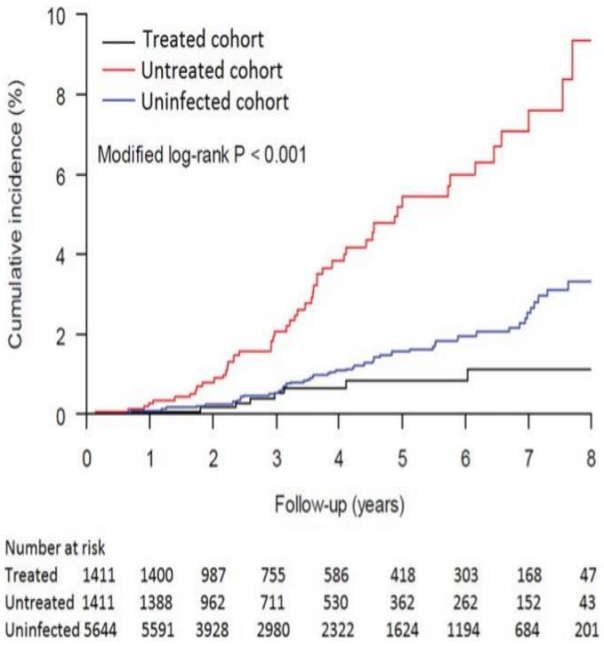
FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IGC, improved glycemic control; DAA, direct-acting antiviral agent; NIGC, non-improved glycemic control; SD, standard deviation.

DAWOOD et al, Diabetes Metab J 2017

Antiviral therapy reduces the renal and cardiovascular complications in 9572 chronic hepatitis C patients with diabetes

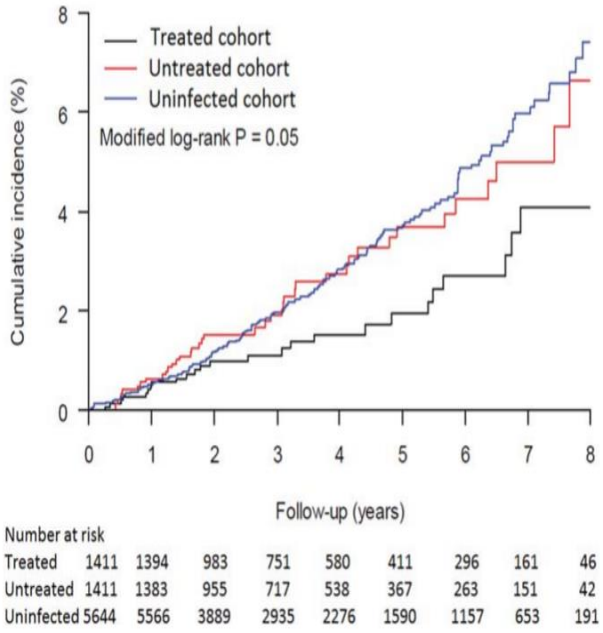
Taiwan National Health Insurance Research Database:
1411 HCV treated *vs.* 1411 HCV untreated *vs.* 5644 uninfected, matched by propensity scores (demographic factors, comorbidities, diabetes therapy)

Cumulative incidence of ESRD



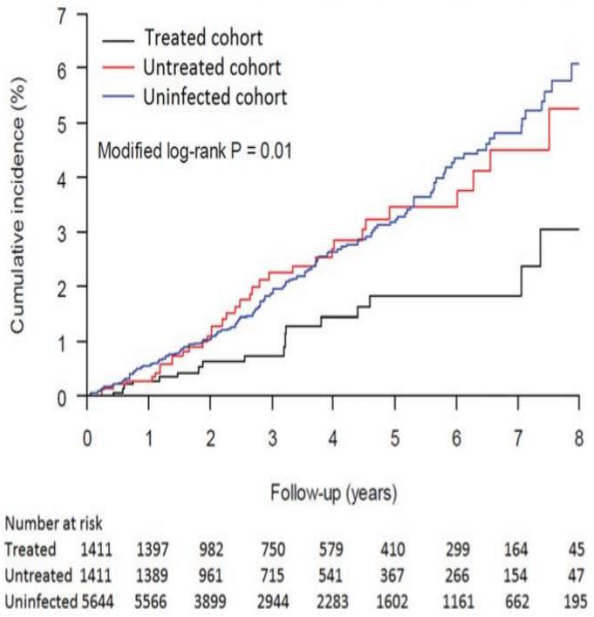
(HR 0.16, 95% CI 0.07 – 0.33)*

Cumulative incidence of acute coronary events



(HR 0.64, 95% CI 0.39 – 1.06)*

Cumulative incidence of ischemic stroke



(HR 0.53, 95% CI 0.30 – 0.93)*

***Multivariate comorbidity-adjusted HR in treated *vs.* untreated cohort**

HSU et al, *Hepatology* 2014;59:1293-302

Risk of HCC in HCV-related *advanced fibrosis after SVR*

Multicenter study on 630 patients with SVR after treatment with (peg)IFN-based therapies

Median FU 5.7 y (IQR 2.9–8.0), 51 incident HCC cases

Predictor of HCC Following SVR*	HR (95% CI)	P
Age at SVR, yrs		
▪ <45	1.00 (reference)	NA
▪ 45-60	8.54 (1.13 – 64.64)	.038
▪ >60	8.91 (1.12 – 70.79)	.039
Diabetes	**2.36 (1.02 – 5.42)**	**.044**
Platelet count	1.04 (1.00 – 1.09)	0.048
AST/ALT ratio	0.56 (0.32 – 1.01)	0.084

VAN DER MEER *et al,* J Hepatol 2017;66:485-93

Predictors of HCC occurrence after SVR, *all fibrosis stages*

VA cohort study, 22,028 HCV pts treated with PegIFNα ± RBV between 1999 and 2009
HCC incidence (x 1000 PY): 3.27 SVR vs 13.2 non SVR (HR: 0.358)

Predictor of HCC Following SVR*	HR (95% CI)	P
Cirrhosis	4.45 (2.53-7.82)	< .0001
Age at SVR, yrs (vs. younger than 55 yrs)		
▪ 55-64	2.40 (1.53-3.77)	.0002
▪ 65 or older	4.69 (2.04-10.78)	.0003
Diabetes	**2.07 (1.35-3.20)**	**.0010**
HCV genotype (vs. genotype 1)		
▪ HCV-2	0.56 (0.32-1.01)	.0522
▪ HCV-3	1.91 (1.14-3.18)	.0131

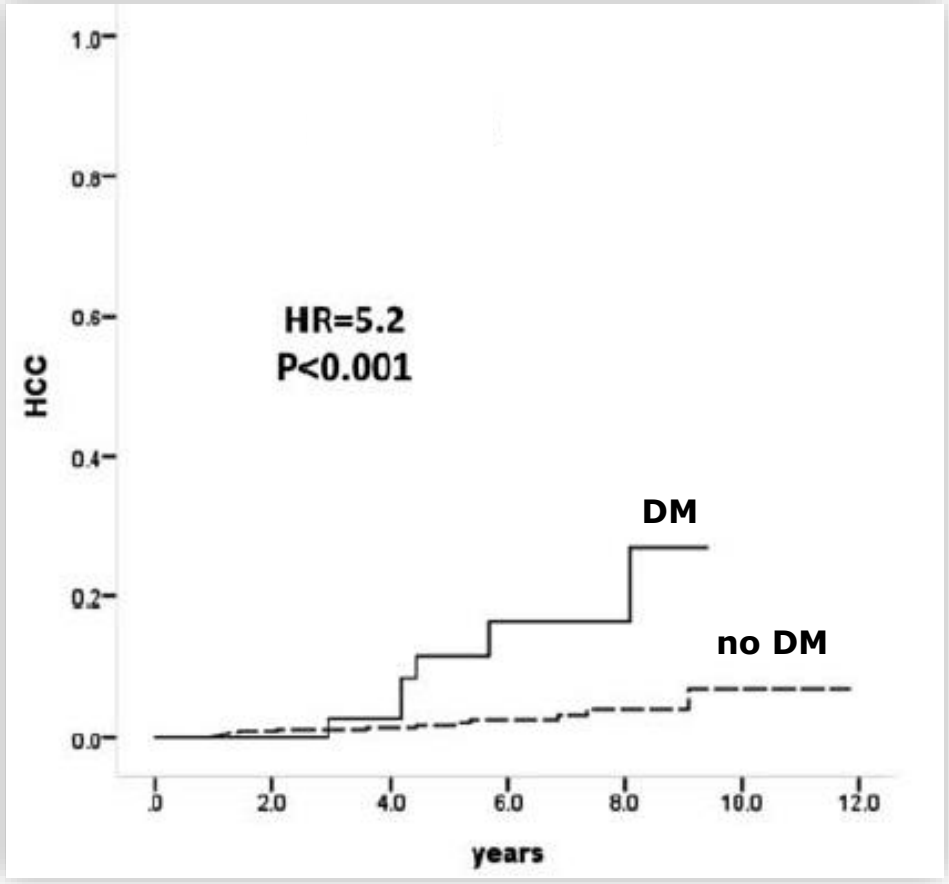
*Cox proportional hazards model adjusted for competing risk of death

EL-SERAG *et al,* Hepatology 2016;64:130-7

Diabetes before antiviral therapy (together with age and low platelet count) predicts HCC occurrence after SVR

*also in patients with F0-F2**

(n=1112, FU 55.9 months; 93 incident HCC at a yearly rate of 1.79%; Kaohsiung MUH, Taiwan)

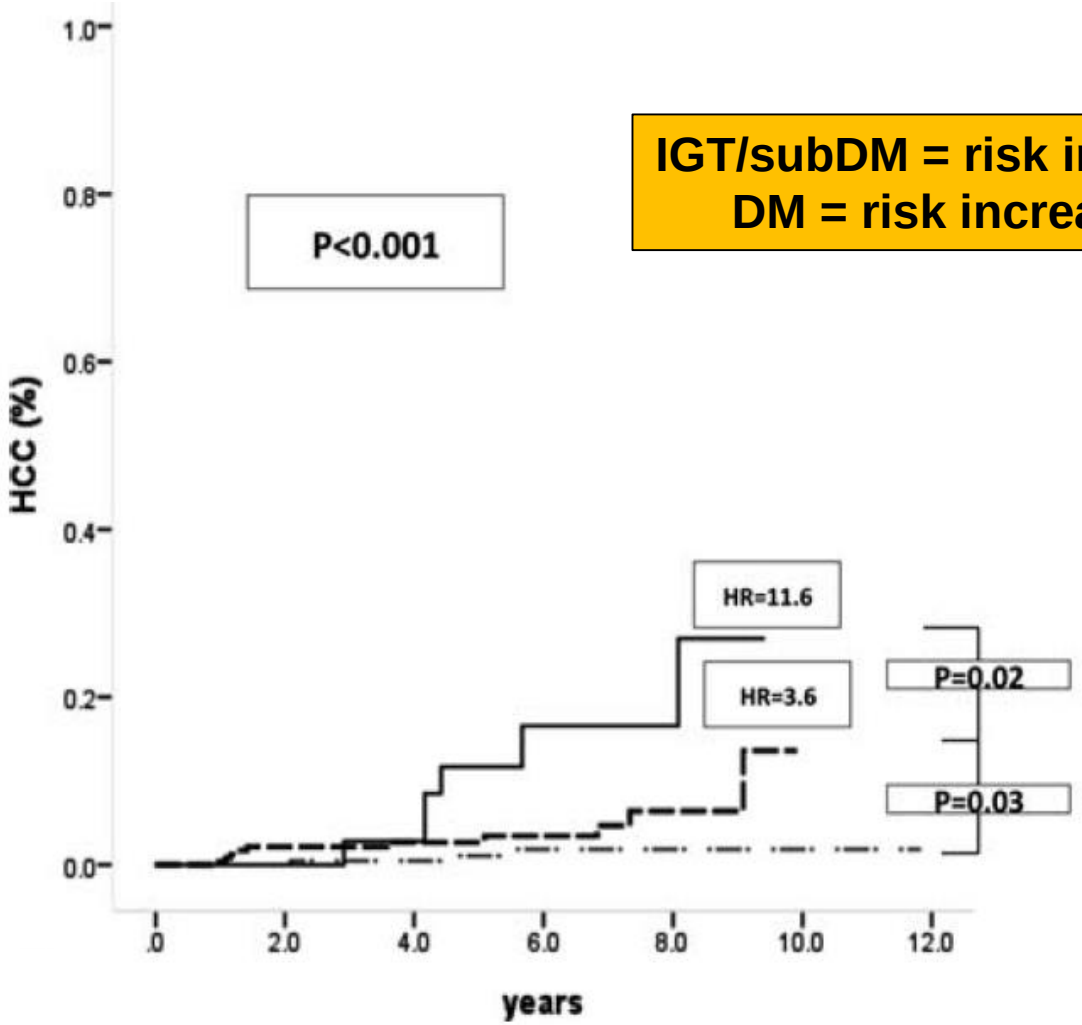


*DM or lack thereof did not affect HCC rate in non-SVR or F3-F4

HUANG *et al,* Medicine 2016;95:27(e4157)

Most F0-F2 patients who developed HCC despite SVR had glucose metabolism alterations before therapy

(and despite improved glucose homeostasis after SVR)



IGT/subDM = risk increased 3-fold
DM = risk increased 10-fold

6/54 if DM (11.1%)

10/268 if IGT/subDM (3.7%)

3/267 if normoglycemic (1.1%)

HUANG *et al*, Medicine 2016;95:27(e4157)

Cardiovascular disorders

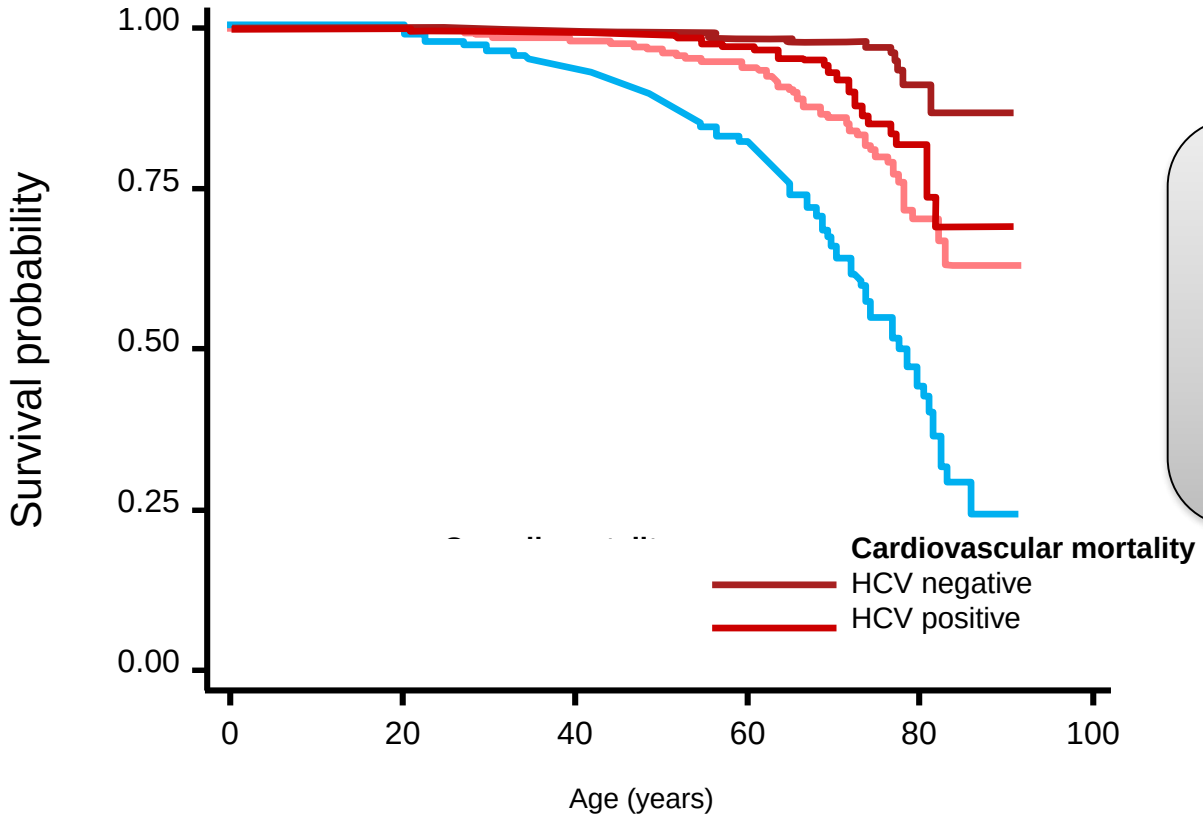
Classical CVD risk factors may be absent in HCV

	Never HCV infected (n=585)	Past HCV infection (n=67)	Chronic HCV infection (n=113)
BMI (kg/m^2)	27.5 (5.91)	28.9 (5.49)	27.4 (5.75)
WHR	0.88 (0.08)	0.90 (0.07)	0.91 (0.09)
SBP (mm Hg)	124.2 (20.4)	128.0 (26.8)	125.2 (22.9)
DBP (mm Hg)	80.4 (11.4)	82.1 (13.6)	81.2 (12.1)
Fasting glucose (mg/dl)	85.6 (25.4)	91.3 (32.5)	92.7 (42.4)
Total cholesterol (mg/dl)	181.2 (40.6)	189.2 (38.4)	160.4 (33.1)
LDL cholesterol (mg/dl)	109.9 (36.8)	114.5 (36.3)	93.4 (30.9)
HDL cholesterol (mg/dl)	47.2 (11.1)	46.7 (10.5)	46.7 (12.1)
Triglycerides (mg/dl)	121.0 (66.2)	140.3 (65.0)	101.9 (45.1)

MARZOUK *et al*, Gut 2007;56:1105-10

Increased overall and cardiovascular mortality in blood donors according to anti-HCV status

A retrospective US cohort study

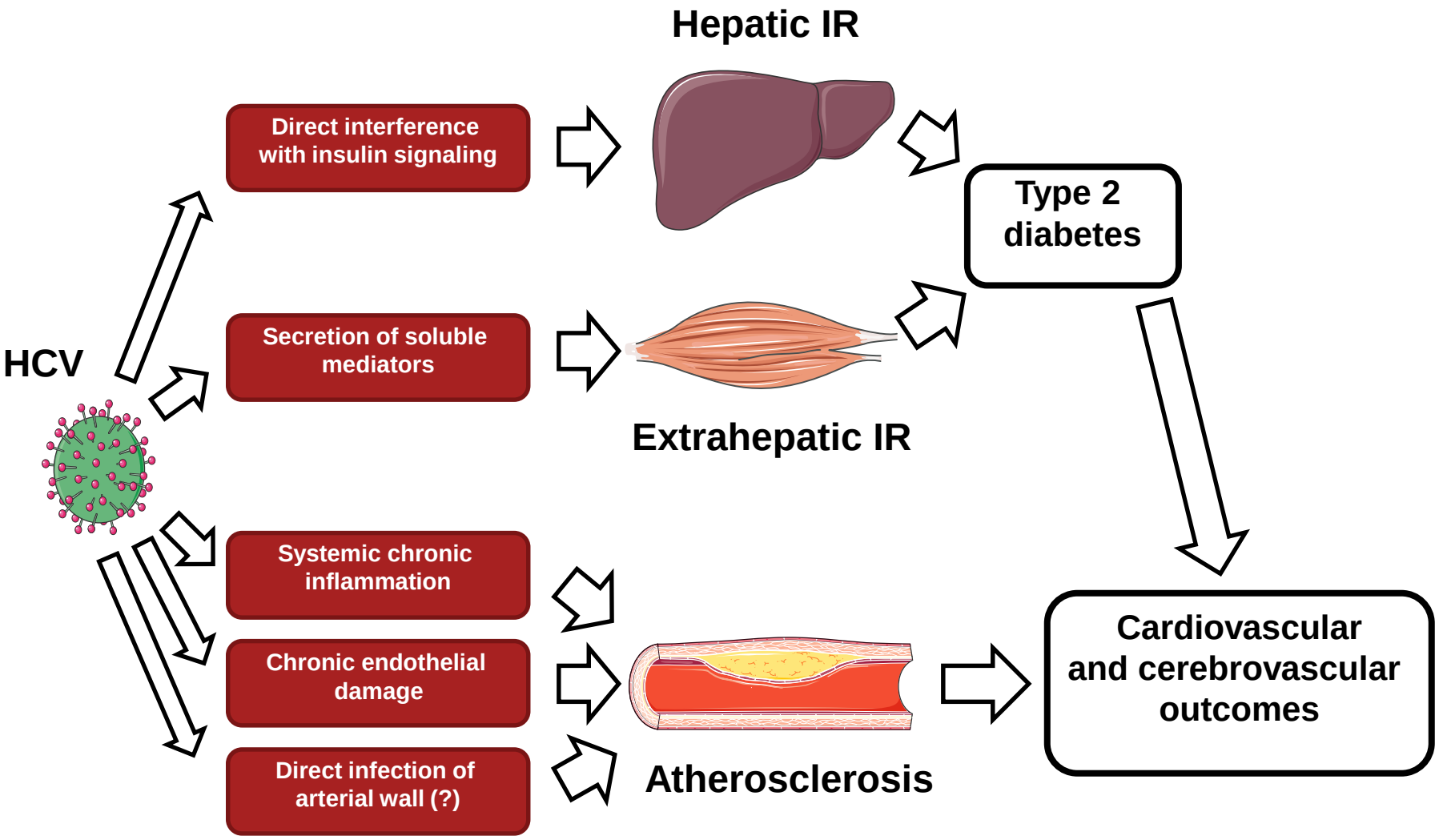


10,259 HCV+ *vs*
10,259 HCV-
age and sex-matched
blood donors
(mean FU 7.7 years)

Cardiovascular mortality (HR 2.21, 95% CI 1.41 – 3.46)

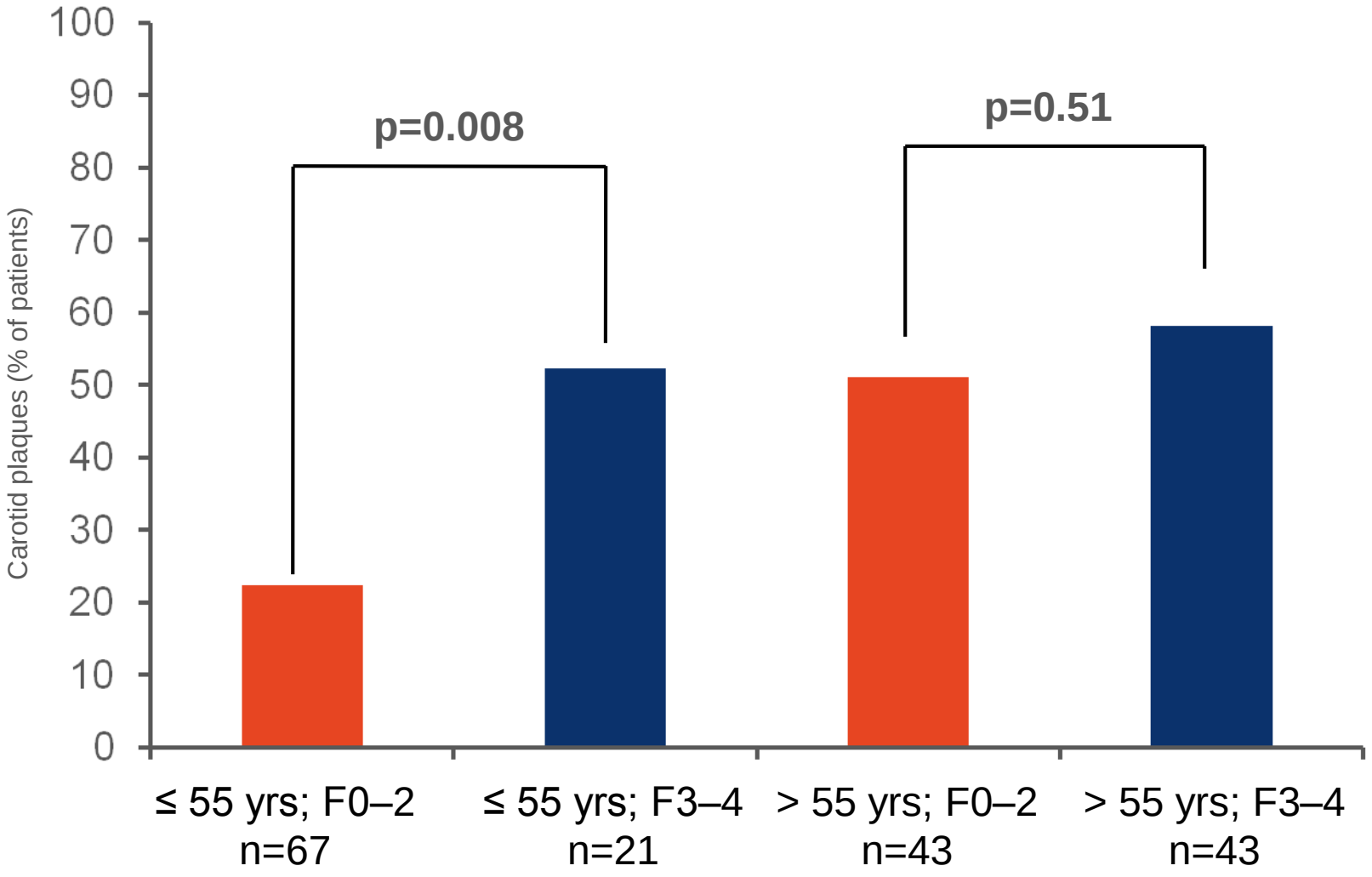
GUILTINAN *et al,* Am J Epidemiol 2008;167:743–750

HCV and cardiovascular outcomes



Carotid atherosclerosis and chronic hepatitis C
A prospective study of risk associations

Prevalence of carotid plaques according to age and fibrosis, HCV-1



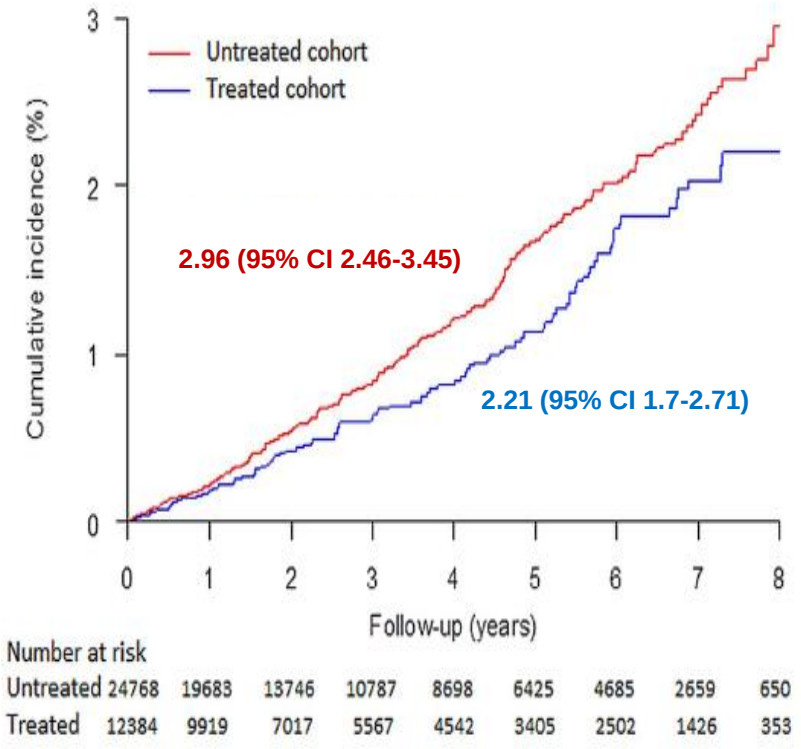
PETTA *et al,* Hepatology 2012;55:1317–1323

Effect of antiviral treatment on cardiovascular outcomes

Taiwan National Health Insurance Research Database (NHIRD)

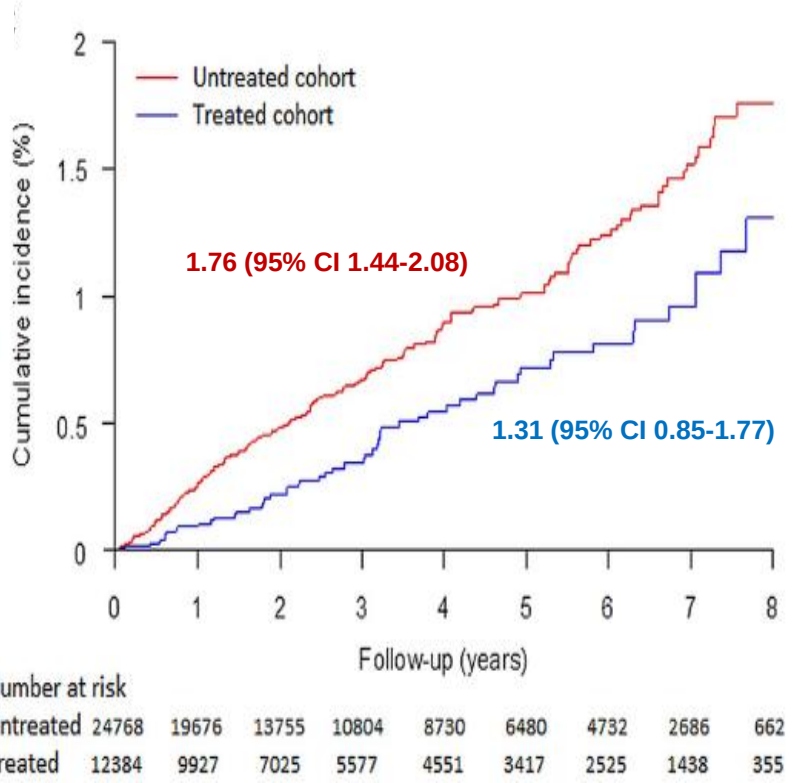
(n=12,384 treated with pegIFN/RBV *vs.* 24,768 untreated controls, matched by propensity scores and length of FU)

Cumulative incidence of acute coronary events



P=0.027

Cumulative incidence of ischemic stroke

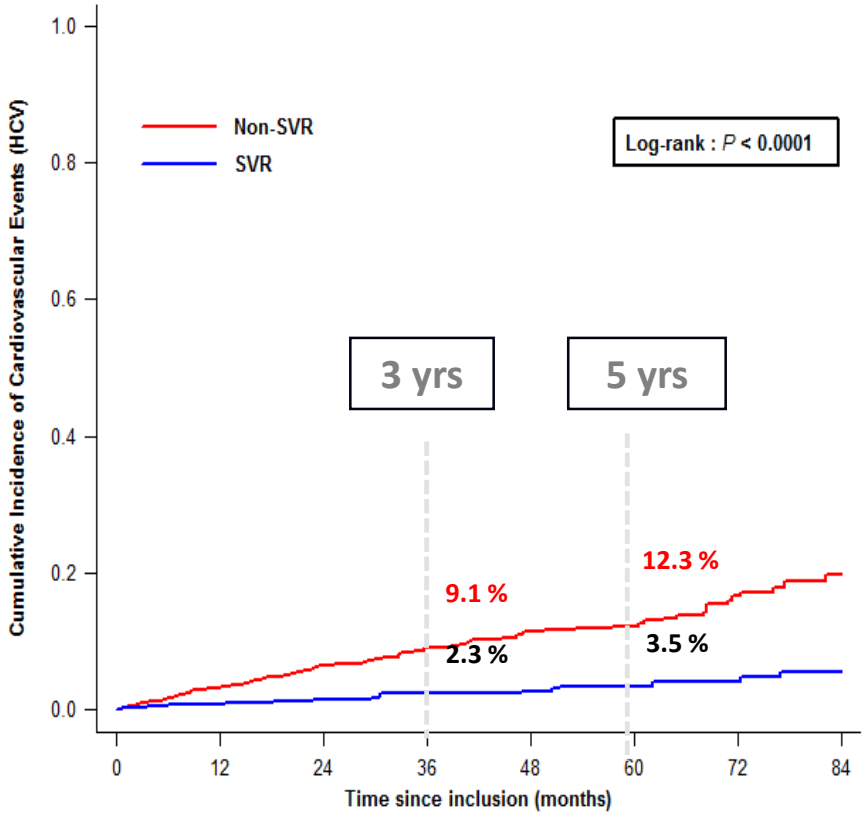


P=0.001

HSU *et al,* Gut 2015;64:495-503

Reduction in cardiovascular events after HCV eradication in patients with cirrhosis

(ANRS CO12 CirVir prospective cohort study, 2012-2015, n=1323, FU 51 mos)

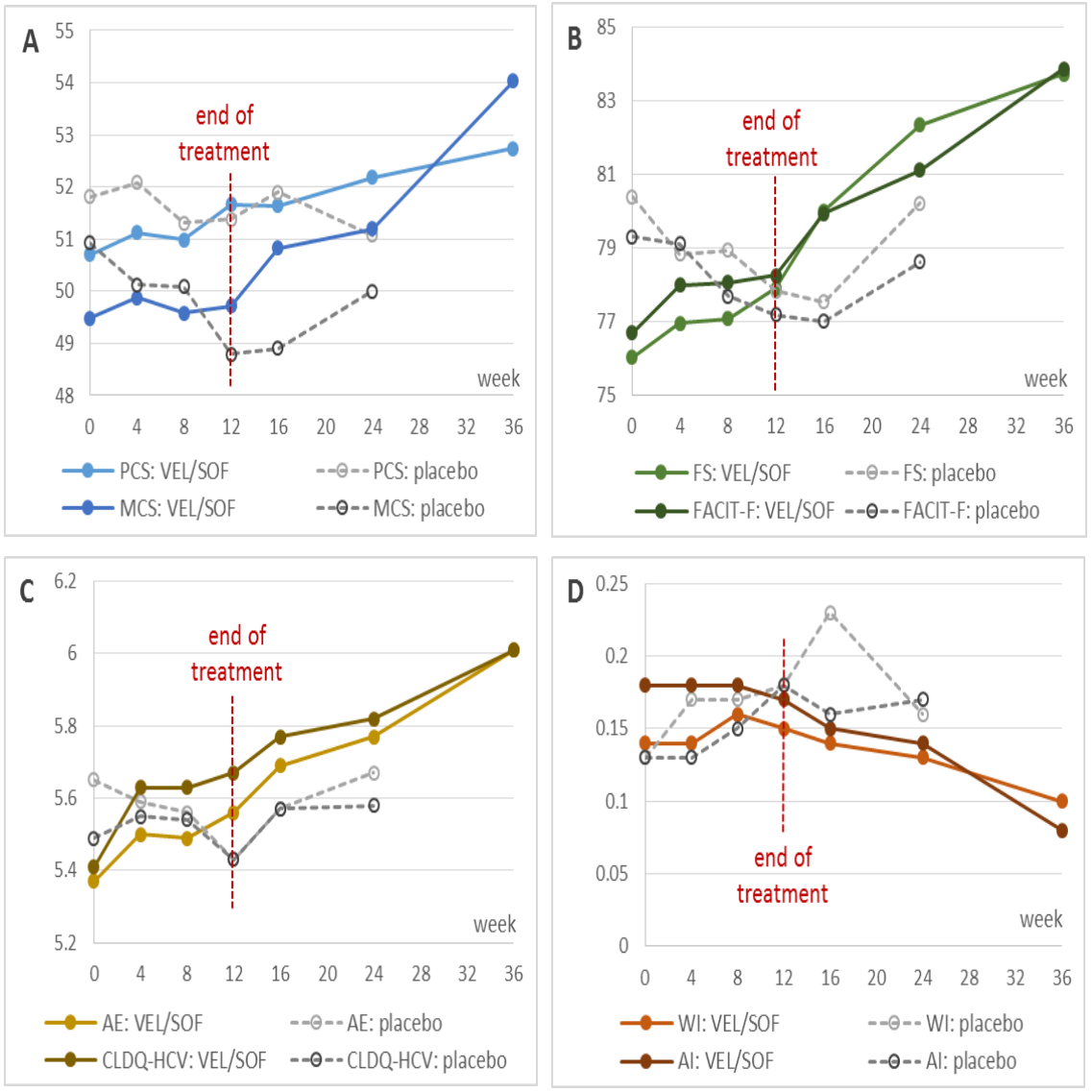


	At-risk patients (events)														
Non-SVR	747	(23)	668	(22)	580	(14)	463	(10)	344	(3)	243	(9)	138	(4)	68
SVR	474	(4)	453	(3)	410	(3)	337	(1)	264	(2)	201	(1)	137	(2)	57

NAHON *et al,* Gastroenterology 2015

Patients’ reported outcomes

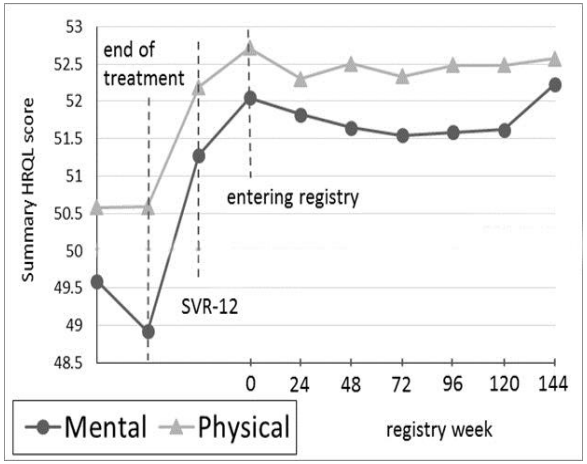
SOF-VEL improves PRO *vs.* placebo in HCV-1, -2, -4, -5 and -6, even after SVR12 (ASTRAL-1 Study)

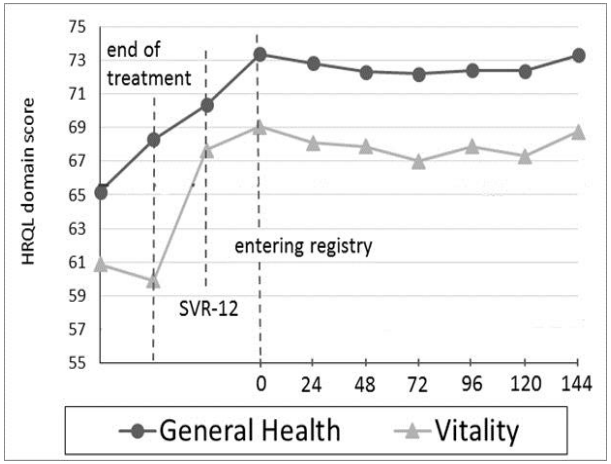


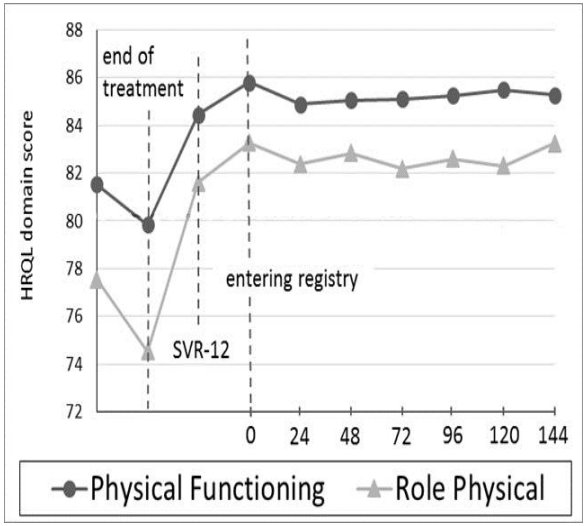
YOUNOSSI *et al*, J Hepatol 2016;65:33-9

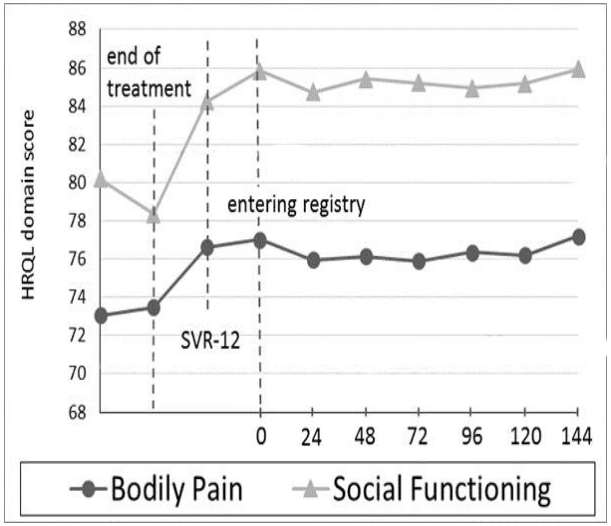
Significant and Sustained Improvement of Health-Related Quality of Life Scores in Patients with Chronic Hepatitis C and SVR

(n=3486 patients from Gilead-sponsored trials' long-term FU registry)









YOUNOSSI *et al*, AASLD 2017

The economic burden of HCV-associated EHM

The HCV health burden deriving from EHM

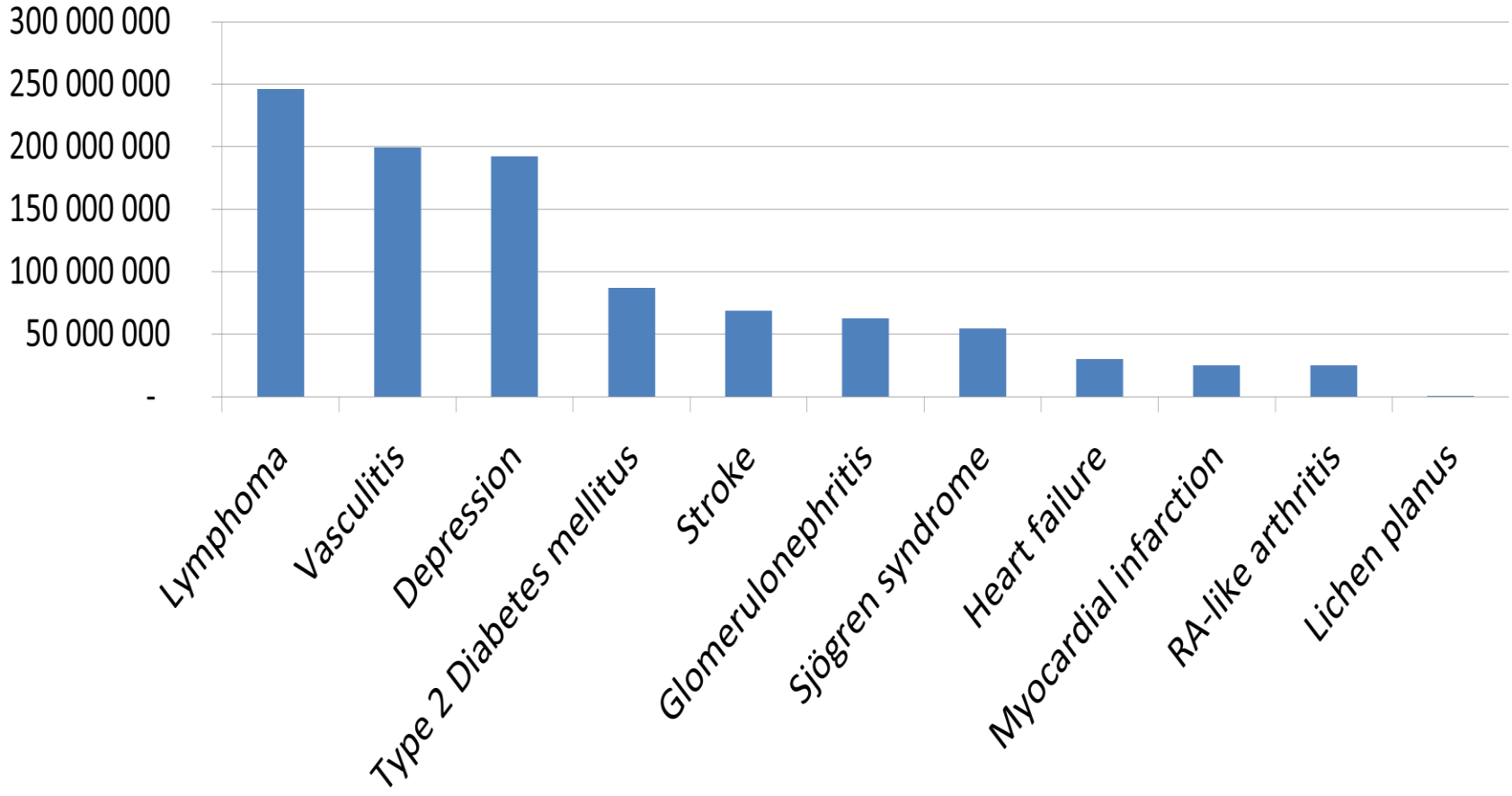
- Meta-analysis on 102 studies
- Total direct costs (2014 USD): 1,506 million (range 922 – 2,208 million USD):
  - 443.4 million USD: type 2 diabetes
  - 430.7 million USD: depression
  - 197.5 million USD: cardiovascular diseases
  - 120.3 million USD: MC

YOUNOSSI *et al*, Gastroenterology 2016;150:1599-1608

Indirect costs are not factored in (significant!)

Difficult to dissect true EHM from comorbidities

Total annual direct costs of extrahepatic manifestations of HCV
(France, € 2015)



CACOUB *et al*, Aliment Pharmacol Ther 2018 (in press)

Estimation of total reduction in annual direct costs associated with extrahepatic manifestations of HCV infection, assuming all treated patients are cured

	GER	ESP	ITA	UK	FRA
T2D	€ 18,582,578	€ 24,128,753	€ 38,683,580	€ 8,308,169	€ 14,005,942
Mixed cryoglobulinemia	€ 17,568,866	€ 30,473,132	€ 53,723,731	€ 7,533,195	€ 8,683,977
Myocardial infarction	€ 4,908,364	€ 5,810,333	€ 27,522,350	€ 3,822,495	€ 2,643,785
ESRD	€ 4,098,825	€ 4,572,750	€ 14,126,609	€ 1,888,642	€ 2,427,717
Stroke	€ 5,244,957	€ 4,499,332	€ 11,077,101	€ 1,361,283	€ 1,444,554
TOTAL	**€ 50,403,591**	**€ 69,484,300**	**€ 145,133,371**	**€ 22,913,784**	**€ 29,205,975**

CACOUB *et al,* J Viral Hep 2018 (in press)

HCV-associated extrahepatic manifestations and SVR
Take home messages

- HCV is associated with significant extrahepatic morbidity and mortality
- Clearance of HCV is associated with improved extrahepatic morbidity and mortality, and reduced economic burden
- There is some evidence that viral clearance should be achieved early during the natural history of infection
- Chronic hepatitis C patients should be screened for signs of extrahepatic involvement (eGFR, glucose metabolism alterations, carotid plaques) even at early stages of liver disease, and treated