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8th
PARIS
HEPATITIS
CONFERENCE

12 & 13 January 2015
PARIS - Palais des Congrès

Patients with chronic hepatitis C and comorbidities

Optimal management of patients with chronic hepatitis C and comorb... ...DAA's

JE SUIS CHARLIE

Optimal management of patients with chronic hepatitis C and comorbidities in the era of IFN-FREE all-Oral DAA's

Key points

- Impact of comorbidities on the natural history of chronic HCV infection

- Does comorbidities impact on SVR achievement?

- Does SVR impact in improving comorbidities?

- Will wide-spread use of treatment in patients with severe comorbities impact on overall survival?

Optimal management of patients with chronic hepatitis C and comorbidities in the era of IFN-FREE all-Oral DAA's

Key points

• Impact of comorbidities on the natural history of chronic HCV infection

Does comorbitities impact on SVR achievement? N

Does SVR impact in improving comorbidities? YES

Will wide-spread use of treatment in patients with severe comorbities impact on

overall survival?

Factors affecting the progression of HCV-related liver disease

| Not Modifiable	Modifiable without antiviral treatment
Age?	Alcohol consumption
Male sex	Non-alcoholic fatty liver disease
Older age at infection	Metabolic Syndrome
	Insulin resistance/diabetes
	Modifiable with antiviral treatment
	Fibrosis stage
	HCV Genotype
	Cryoglobulinemia/Non-Hodgkin's lymphoma
	Coinfection with HBV or HIV
	Non-alcoholic fatty liver disease/metabolic syndrome
	Insulin resistance/diabetes

Modifiable factors:
Extrahepatic manifestations

| 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%

Modifiable factors:
Extrahepatic manifestations

Chronic HCV increases mortality from hepatic and non-hepatic diseases
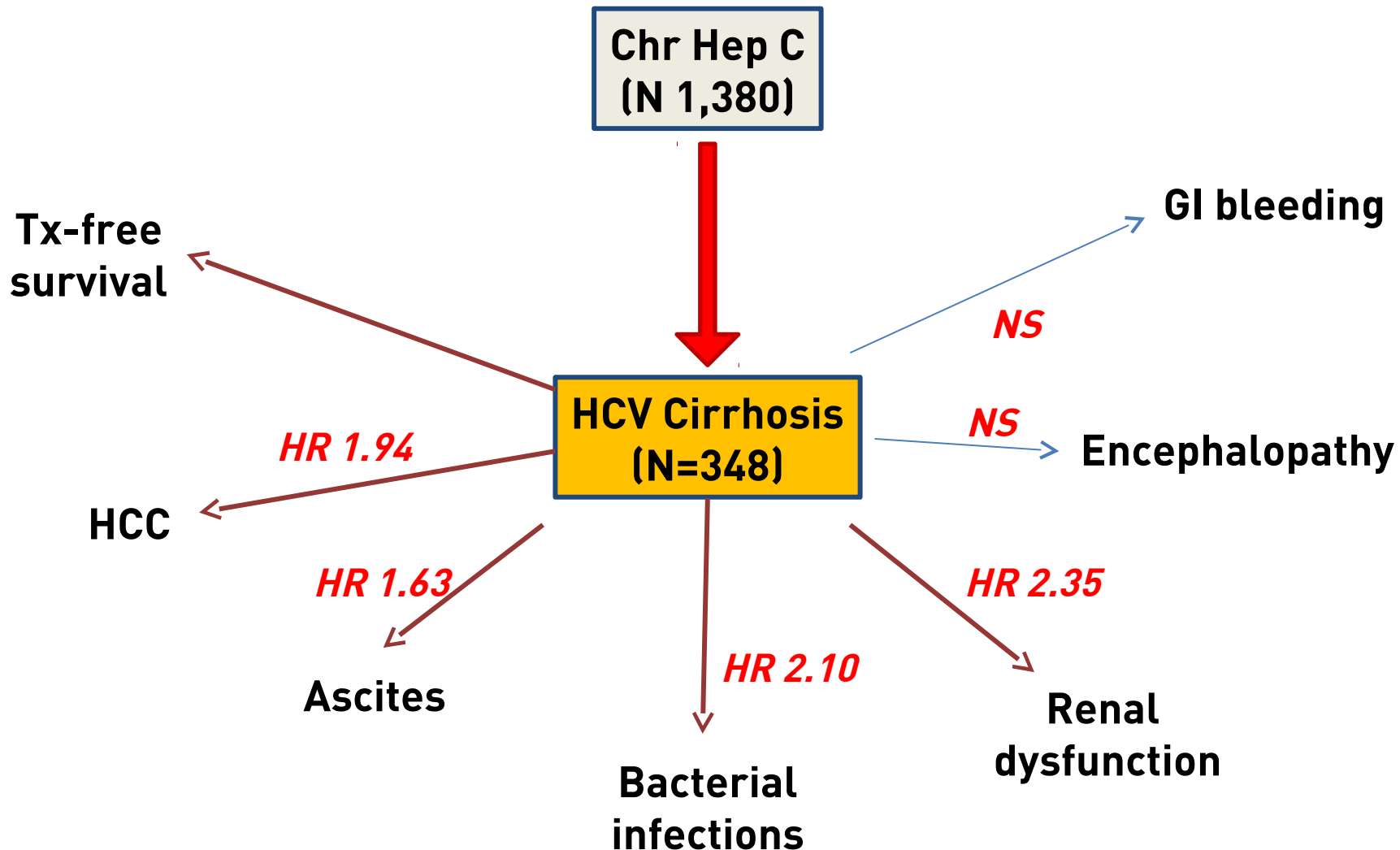**The REVEAL HCV Cohort Study**
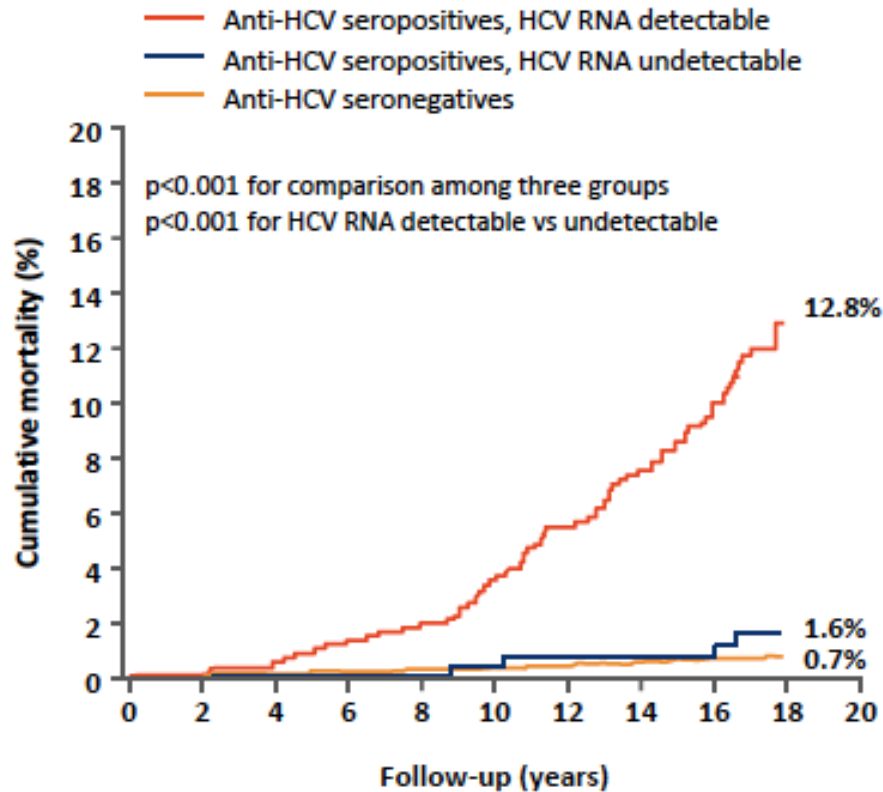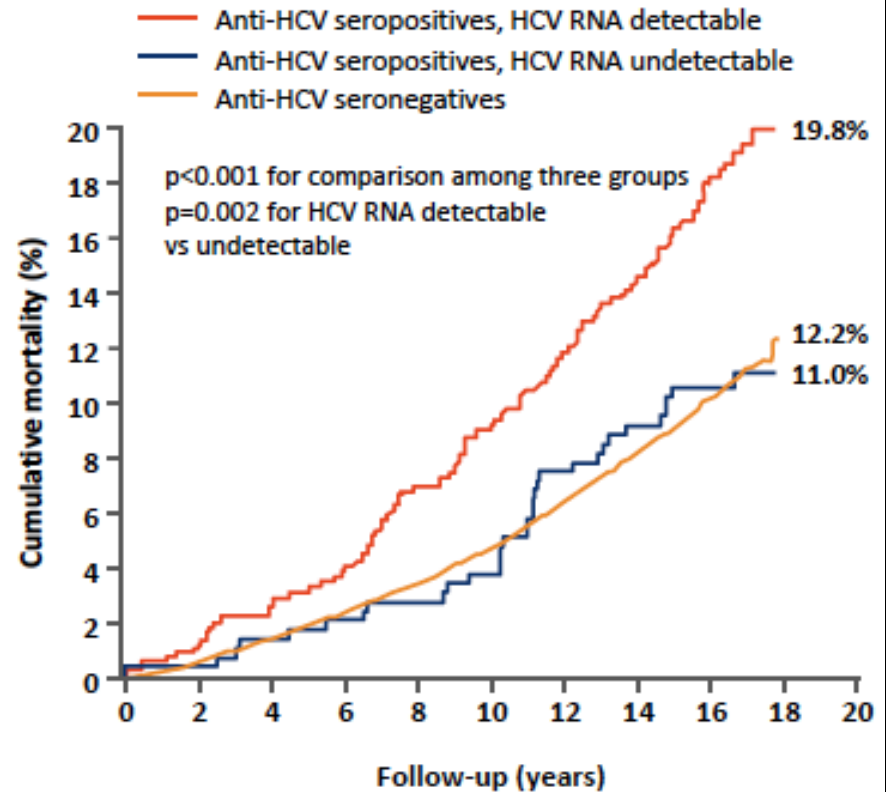
Modifiable (± antiviral therapy) factors: Insulin resistance/Diabetes

Diabetes precipitates progression to cirrhosis and its complications
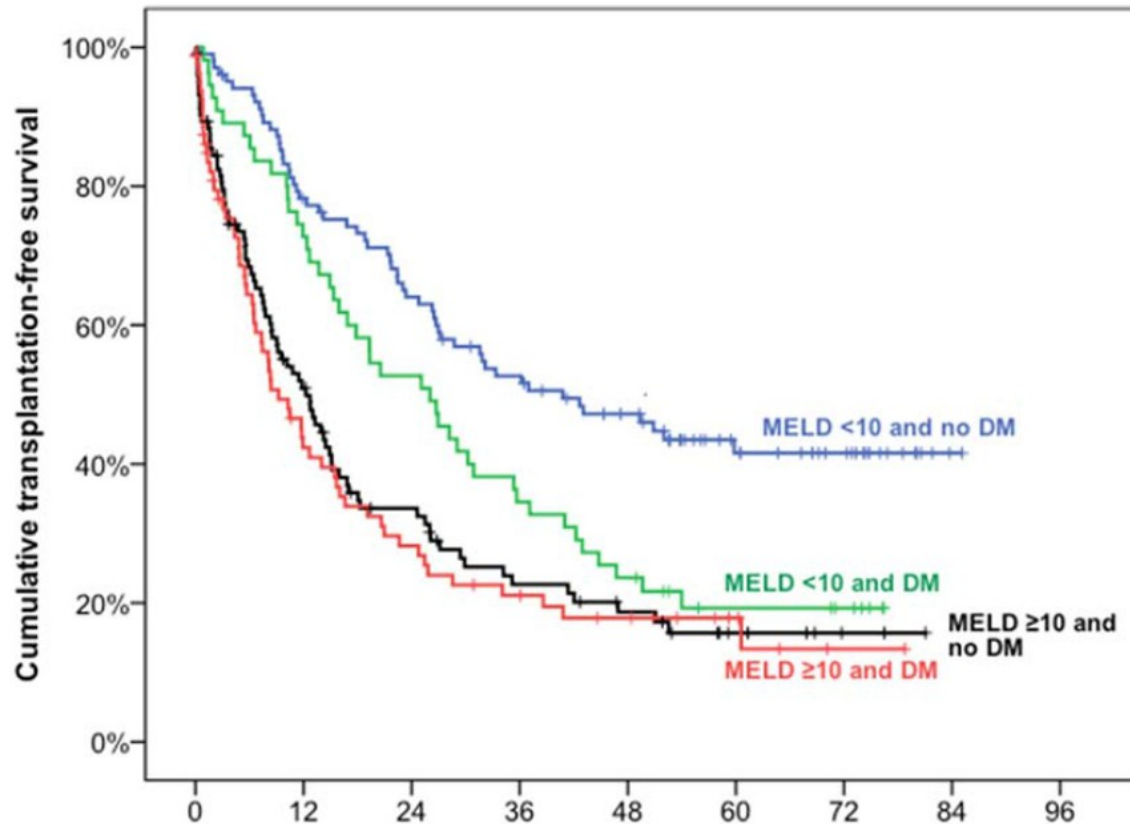

El Krief, Hepatology 2014

Modifiable (± antiviral therapy) factors:
Insuline resistance/Diabetes

Diabetes precipitates progression to cirrhosis and its complications
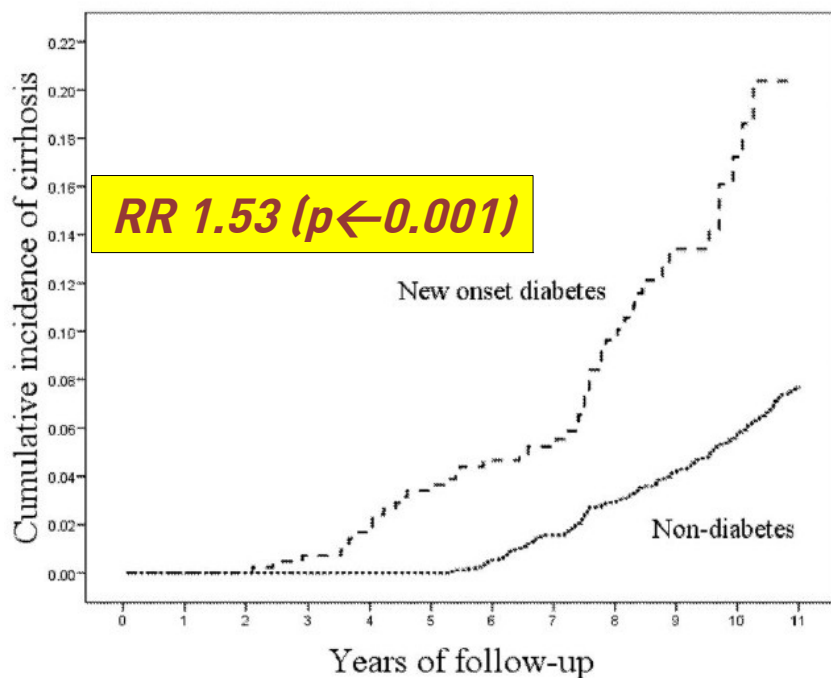

El Krief, Hepatology 2014

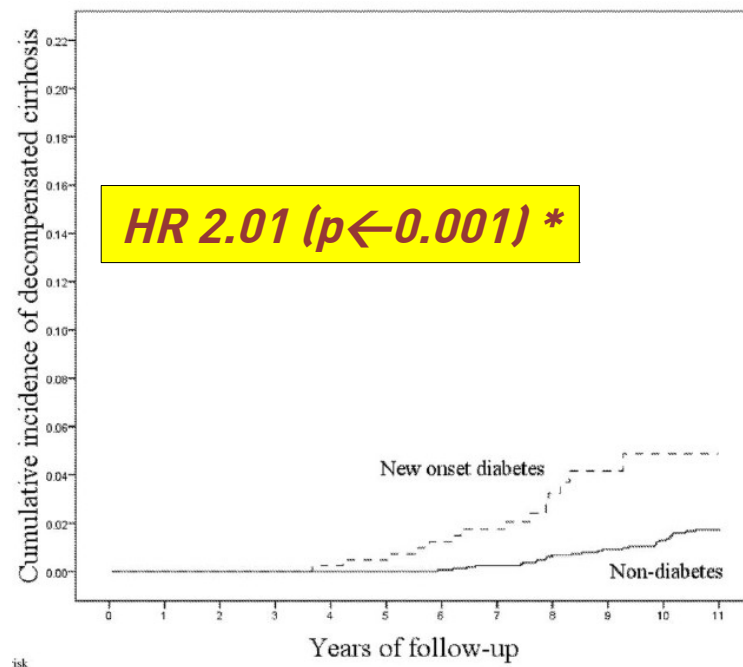# Modifiable (± antiviral therapy) factors: Insulin resistance/Diabetes

Diabetes accelerates cirrhosis occurrence and its decompensation

424 HCV + new onset diabetes in Taiwan
1,708 HCV + non diabetics
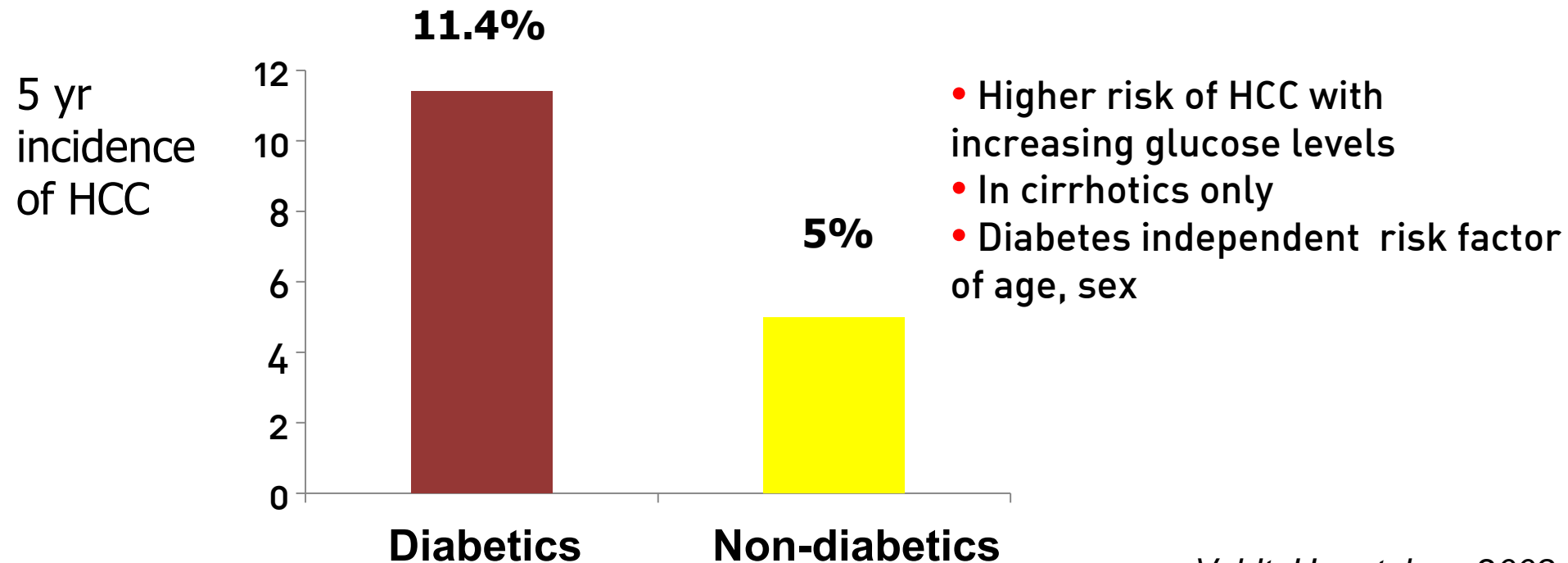
CIRRHOSIS OCCURENCE

CIRRHOSIS DECOMPENSATION

RR 1.53 (p←0.001)

HR 2.01 (p←0.001) *

* Adjusted HR 3.56 on age, sex, comorbidity index, obesity, hyperlipidemia, treatment

Huang, Hepatology 2014

Modifiable (± antiviral therapy) factors: Insulin resistance/Diabetes

Diabetes increases HCC risk in HCV patients

N=541 HCV patients (Germany, Canada, Holland, Switzerland)
Ishak 4-6; median f/u 4 years

5 yr incidence of HCC

11.4%

5%

Diabetics   **Non-diabetics**

- Higher risk of HCC with increasing glucose levels
- In cirrhotics only
- Diabetes independent risk factor of age, sex

Veldt, Hepatology 2008

Modifiable (± antiviral therapy) factors:
Insulin resistance/Diabetes

Impact of Diabetes and Overweight on Liver Cancer Occurence in Cirrhosis

84%

38%

OLE

BMI <23.9, diabetes −

BMI <23.9, diabetes +

BMI 23.9-27.3 diabetes −

BMI 23.9-27.3 diabetes +

BMI >27.3, diabetes −

BMI >27.3, diabetes +

N = 771

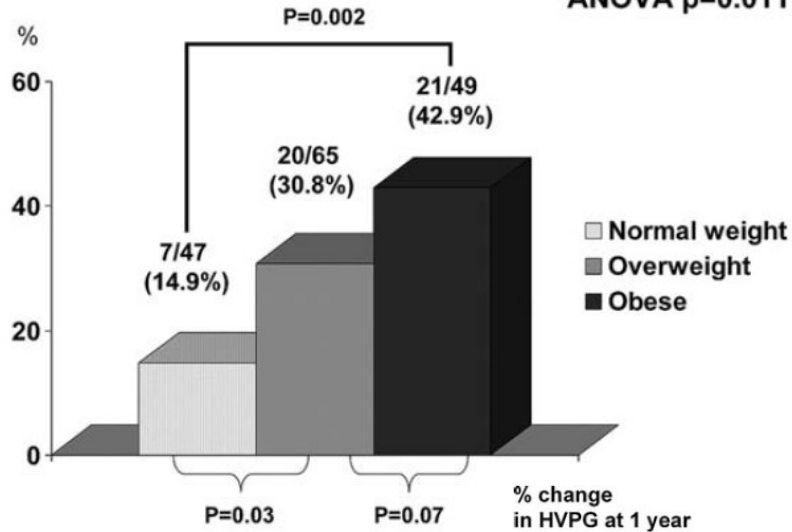*N'Kontchou, Clin Gastro Hepatol 2006*

Modifiable (without antiviral therapy) factors: Metabolic syndrome

BMI is an independent predictor of cirrhosis decompensation

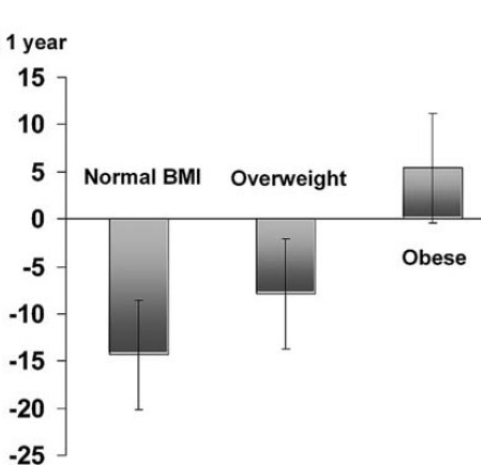*161 compensated cirrhotics with HVPG↑10 mmHg*

Probability first decompensation

% decompensation

ANOVA p=0.011

P=0.002

21/49 (42.9%)

20/65 (30.8%)

7/47 (14.9%)

☐ Normal weight
▨ Overweight
■ Obese

P=0.03   P=0.07

% change in HVPG at 1 year

% change HVPG at 1 year

Normal BMI   Overweight   Obese
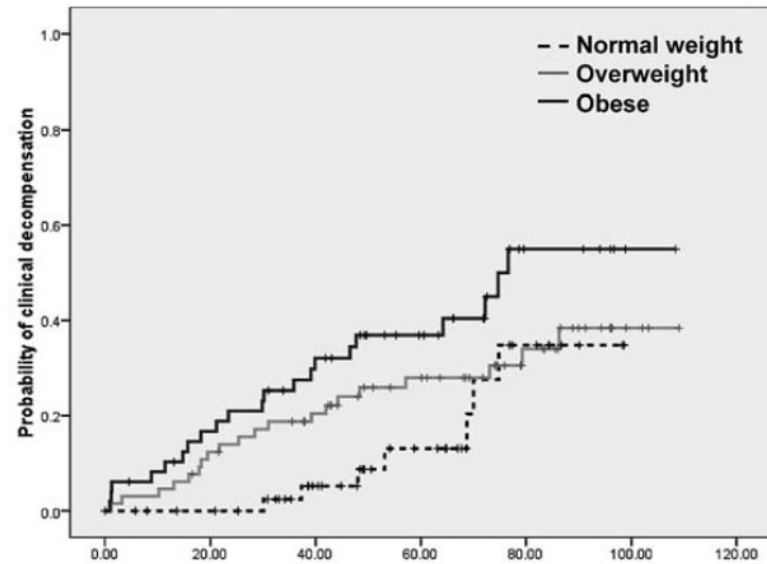
Patients at risk	0	12	24	36	48	60	72	84	96	108
	47	45	40	35	27	18	10	6	2	0
	65	62	54	50	41	35	28	17	8	1
	49	43	37	32	26	20	14	6	4	1

Berzigotti, Hepatology 2011

Modifiable (with antiviral therapy) factors:
Genotype

Cumulative incidence of cirrhosis (A) and HCC (B) in patients with HCV G1, 2, 3 and 4
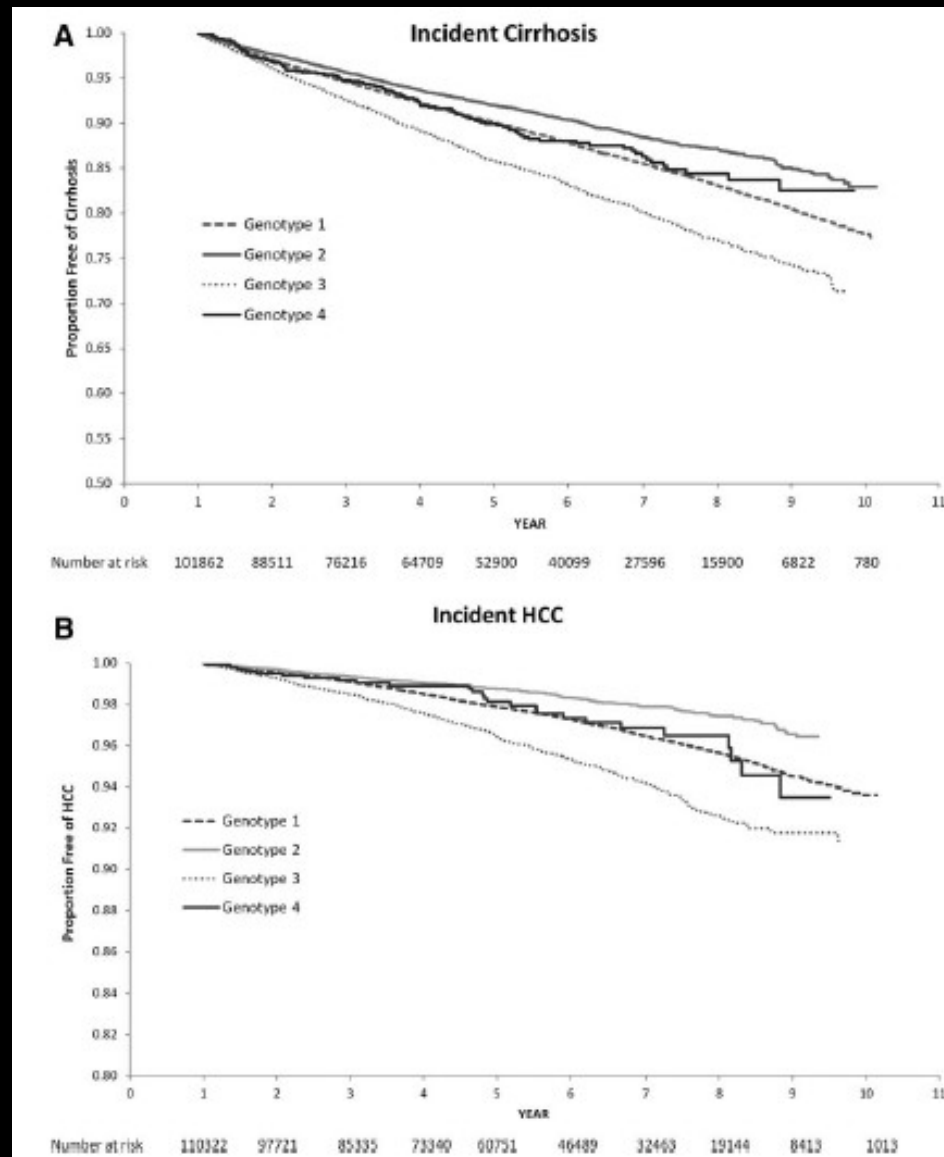
Kanwal F, et al. Hepatology 2014

Optimal management of patients with chronic hepatitis C and comorbiditities in the era of IFN-FREE all-Oral DAA's

Key points

- Does comorbidities impact on SVR achievement?

Not Modifiable factors:
Older Age

The lesson from IFN-based therapy: as effective but more side-effects

Efficacy and safety of PEG-IFN plus RBV in patients aged ↗ 65 years with CHC

Study	Country	Type of Peg-IFN	N. of patients	Overall SVR (%)	G1-4 SVR (%)	G2-3 SVR (%)	Discontinuation rate (%)
Zeuzem et al, 2004	39 European countries	2b	2	50	NA	50	NA
Antonucci et al, 2007	Italy	2a/2b	30	70	36.4	89.5	16.7
Honda et al, 2010	Japan	2b	115	37.4	31.2	63.6	32.2
Huang et al, 2010	Taiwan	2a	70	67.1	51.9	76.7	21.4
Kainuma et al, 2010	Japan	2b	314	31.2	22.9	65.6	36.3
Oze et al, 2011	Japan	2b	240	35.4	27	63.6	23.9
Nishikawa et al, 2012	Japan	2b	108	50	40.7	86.4	13.9
Kim et al, 2012	Korea	2a/2b	38	65.8	30.8	84	21.1
Yu et al, 2012	China	2a	140	42.9	30.5	80	21.1
Hu et al, 2013	Taiwan	2a/2b	91	40.7	32.1	54.3	13.2

First generation DAAs:
Age of patients enrolled in clinical trials utilizing triple therapy with TVR and BOC

Clinical trial	PROVE-1	PROVE-2	PROVE-3	ADVANCE	ILLUMINATE	REALIZE
Median age	49-50	44-46	50-53	49	50-52	50-51
Range (min-max)	21-63	18-65	18-69	18-69	19-70	21-70

| Clinical trial	Sprint-1	Sprint-2	Respond-2
Median age	46.4	NA	52.7
Range (min-max)	NA	38-60	NA

First generation DAAs: Higher risk of anemia

Predictor of serious or hematological adverse events during treatment with BOC (TW5-TW48)

	SERIOUS EVENTS		HEMATOLOGICAL EVENTS	
	Events/patients (%)	OR (95% CI)	Events/patients (%)	OR (95% CI)
Sex				
Men	33/270 (12.2%)	1.00	176/270 (65.2%)	1.00
Women	18/111 (16.2%)	1.39 (0.75-2.59)	89/111 (80.2%)	**2.16 (1.27-3.67)**
Age				
<50 years	10/103 (9.7%)	1.00	60/103 (58.3%)	1.00
50-59 years	21/144 (14.6%)	1.59 (0.71-6.53)	98/144 (68.1%)	1.53 (0.90-2.58)
≥60 years	**19/127 (15.0%)**	**1.64 (0.73-3.69)**	**101/127 (79.5%)**	**2.78 (1.56-4.98)**
METAVIR				
F3	5/121 (4.1%)	1.00	81/121 (66.9%)	1.00
F4	46/260 (17.7%)	**4.99 (1.93-12.9)**	184/260 (70.8%)	1.20 (0.75-1.90)
CHILD class (F4)				
A5	35/220 (15.9%)	1.00	155/220 (70.5%)	1.00
A6	11/ 33 (33.3%)	**2.74 (1.22-6.16)**	25/ 33 (75.8%)	1.34 (0.57-3.11)
Fibroscan				
<12.5 kPa	7/123 (5.7%)	1.00	79/123 (64.2%)	1.00
≥12.5 kPa	37/201 (18.4%)	**3.74 (1.61-8.67)**	145/201 (72.1%)	1.44 (0.89-2.33)
Per 1 kPa increase		1.03 (0.99-1.06)		1.03 (0.99-1.06)
Varices (F4)				
No	26/135 (19.3%)	1.00	94/135 (69.6%)	1.00
Yes	14/ 65 (21.5%)	1.15 (0.56-2.39)	49/ 65 (75.4%)	1.34 (0.68-2.62)
Genotype				
1b	40/296 (13.5%)	1.00	209/296 (70.6%)	1.00
1a	11/ 85 (12.9%)	0.95 (0.47-1.95)	56/ 85 (65.9%)	0.80 (0.48-1.34)
Albumin				
>3.5 g/dL	40/329 (12.2%)	1.00	225/329 (68.4%)	1.00
Low (≤3.5 g/dL)	11/ 52 (21.2%)	**3.42 (1.45-8.08)**	40/ 52 (76.9%)	1.39 (0.57-3.37)

Bruno S, et al. J

RESPONSE TO IFN-BASED THERAPY AND LONG TERM EFFECT OF HCV ERADICATION IN PATIENTS WITH MC WITH OR WITHOUT SYMPTOMS: A PROSPECTIVE, CONTROLLED, OPEN-LABEL, LONG TERM, COHORT STUDY

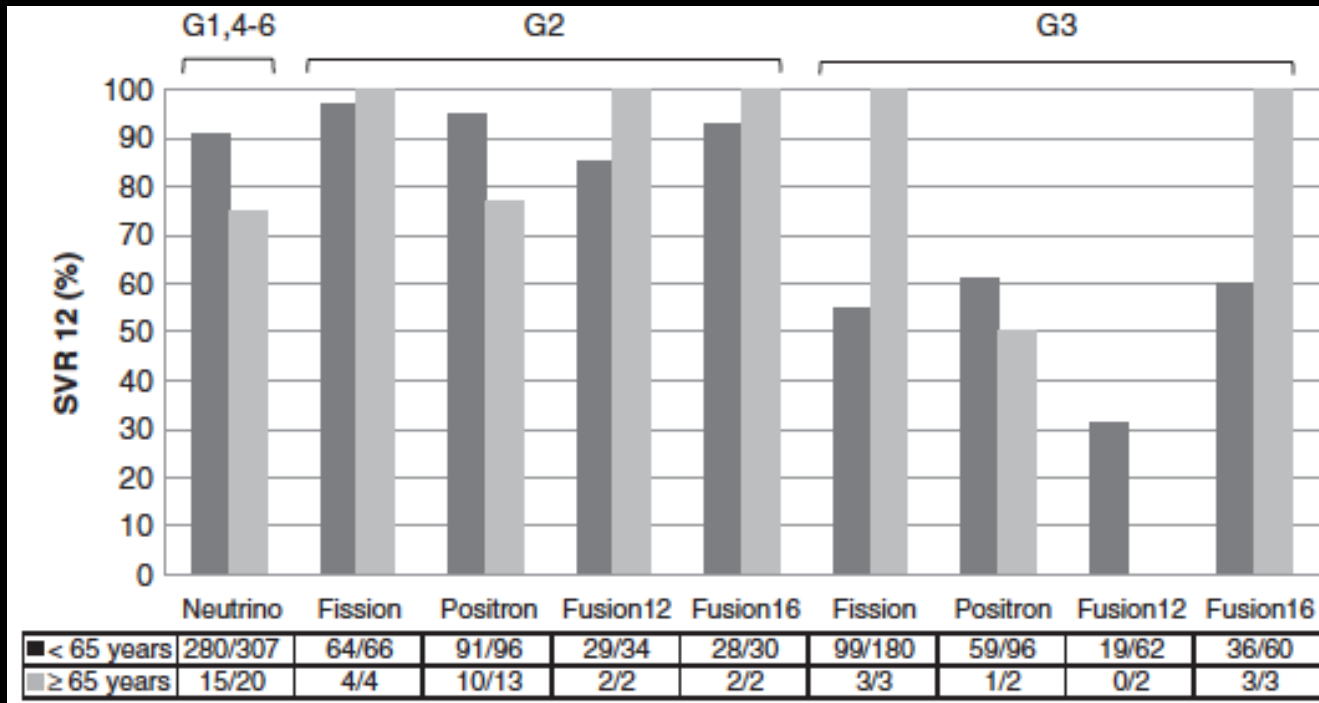## Virological response in HCV patients with and without MC
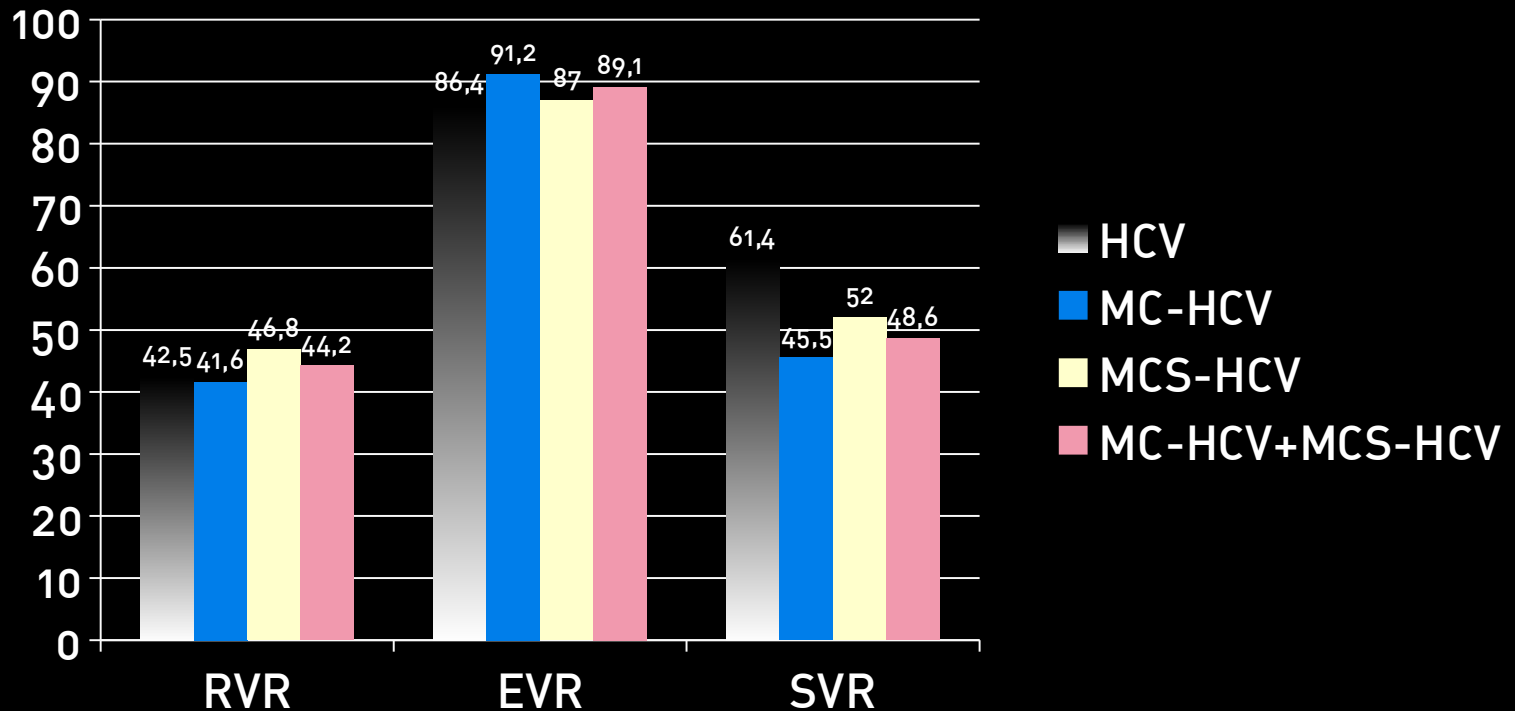
Triple BOC-based antiviral therapy in G1 HCV infection with or without mixed cryoglobulinaemia:
## A prospective, controlled pilot study
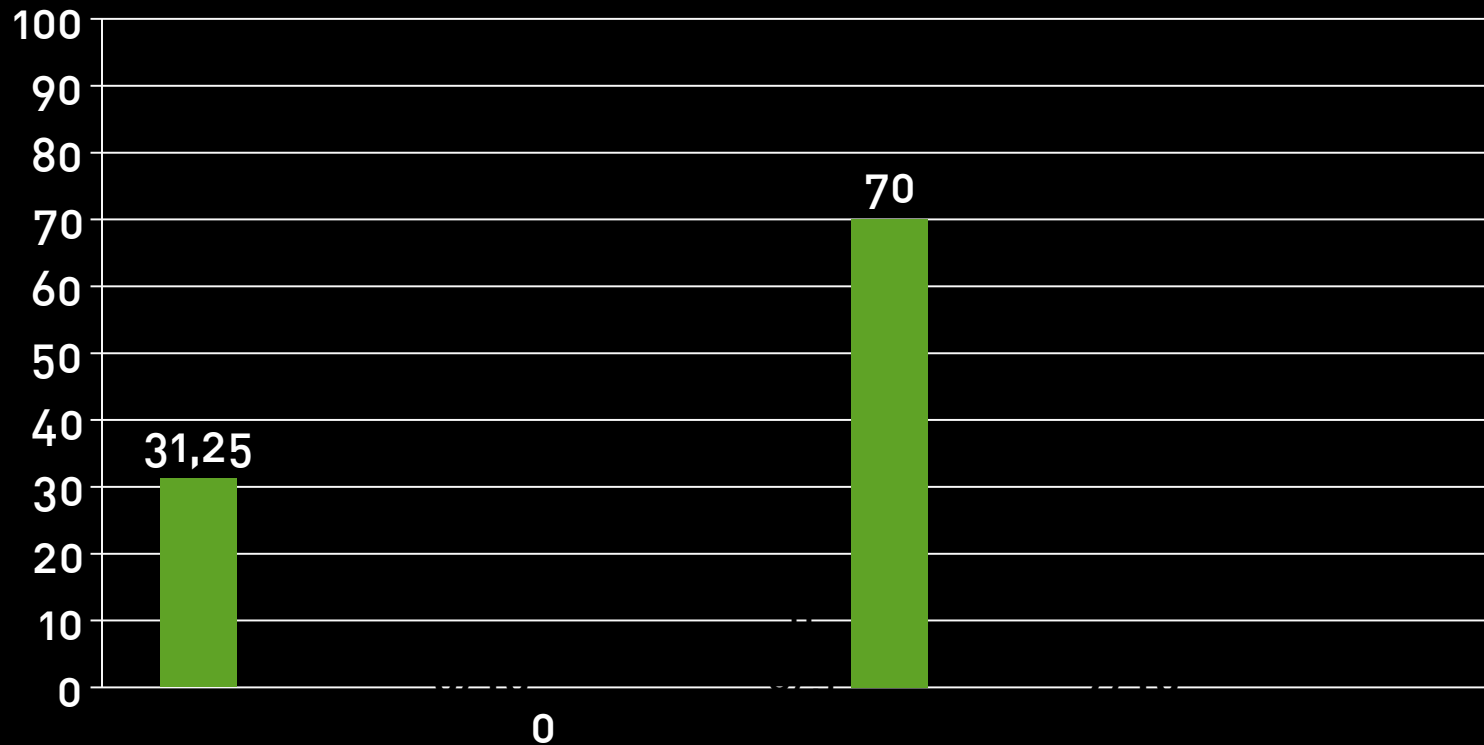
Second generation DAAs

OF	SMV			
Clinical trial	Quest-1	Quest-2	Concerto-1	Promise
Reference	(34)	(35)	(36)	(37)
Median age	48	46	55	52
Range (min–max)	18–73	18–73	23–69	20–70
	SOF			
	Neutrino	Fission	Positron	Fusion
Reference	(38)	(38)	(39)	(39)
Median age	52	48	52	54
Range (min–max)	19–70	20–72	21–75	24–70

	Neutrino	Fission	Positron	Fusion12	Fusion16	Fission	Positron	Fusion12	Fusion16
< 65 years	280/307	64/66	91/96	29/34	28/30	99/180	59/96	19/62	36/60
≥ 65 years	15/20	4/4	10/13	2/2	2/2	3/3	1/2	0/2	3/3

Second generation DAAs

DCV+ASV in G1b naïve or non responders, IFN intolerant/ineligible ± cirrhosis:
## the HALLMARK-DUAL multinational, phase 3, multicohort study
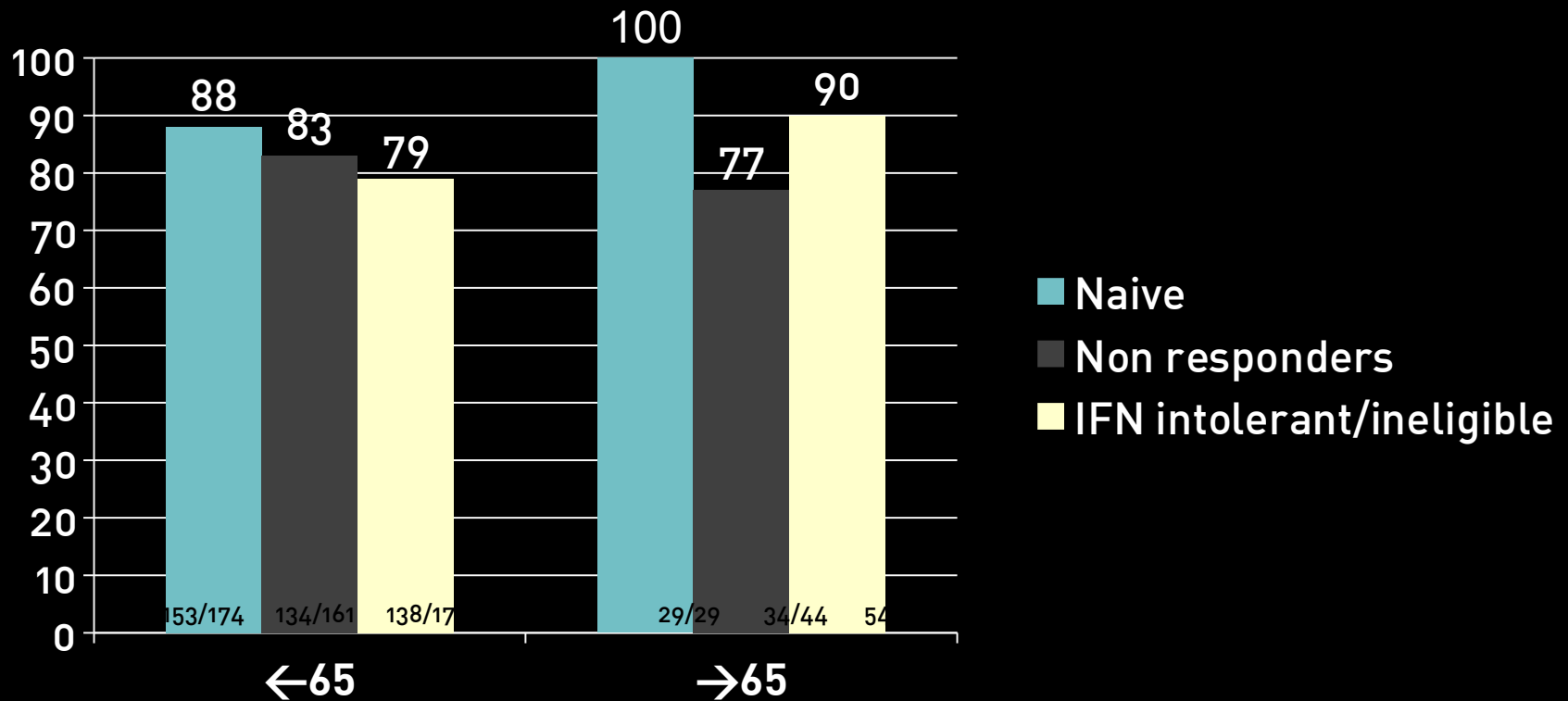
Second generation DAAs

Safety of ABT-450/r/Ombitasvir + Dasabuvir ± RBV in HCV G1 Patients ↗ 65 Years: Results From Phase 2 and 3 Trials

	≥65 years			<65 years		
	3D+RBV n=164 (%)	3D n=50 (%)	Placebo n=23 (%)	3D+RBV n=1880 (%)	3D n=538 (%)	Placebo n=232 (%)
Any AE	154 (93.9)	39 (78)	15 (65.2)	1640 (87.2)	412 (76.6)	181 (78)
Severe AE	8 (4.9)	1 (2)	0	64 (3.4)	10 (1.9)	1 (0.4)
Serious AE	6 (3.7)	1 (2)	0	50 (2.7)	8 (1.5)	1 (0.4)
Grade 3 or 4 AE	9 (5.5)	1 (2)	0	82 (4.4)	14 (2.6)	2 (0.9)
AE leading to discontinuation of study drug	2 (1.2)	0	0	23 (1.2)	2 (0.4)	1 (0.4)
Anemia	21 (12.8)	0	0	118 (6.3)	2 (0.4)	0
Hemoglobin decreased	11 (6.3)	0	0	40 (2.1)	1 (0.2)	0
AE leading to RBV dose modification	27 (16.5)	0	0	131 (7)	1 (0.2)	1 (0.4)

TURQUOISE-II:
ABT-450/r/OMBITASVIR + DASABUVIR +RBV ACHIEVE HIGH SVR12 RATES IN HCV G1-PATIENTS WITH CIRRHOSIS, REGARDLESS OF BASELINE CHARACTERISTICS

TURQUOISE-II: SVR12 Rates by Age and Sex

TURQUOISE-II: ABT-450/r/OMBITASVIR + DASABUVIR +RBV ACHIEVE HIGH SVR12 RATES IN HCV G1-PATIENTS WITH CIRRHOSIS, REGARDLESS OF BASELINE CHARACTERISTICS
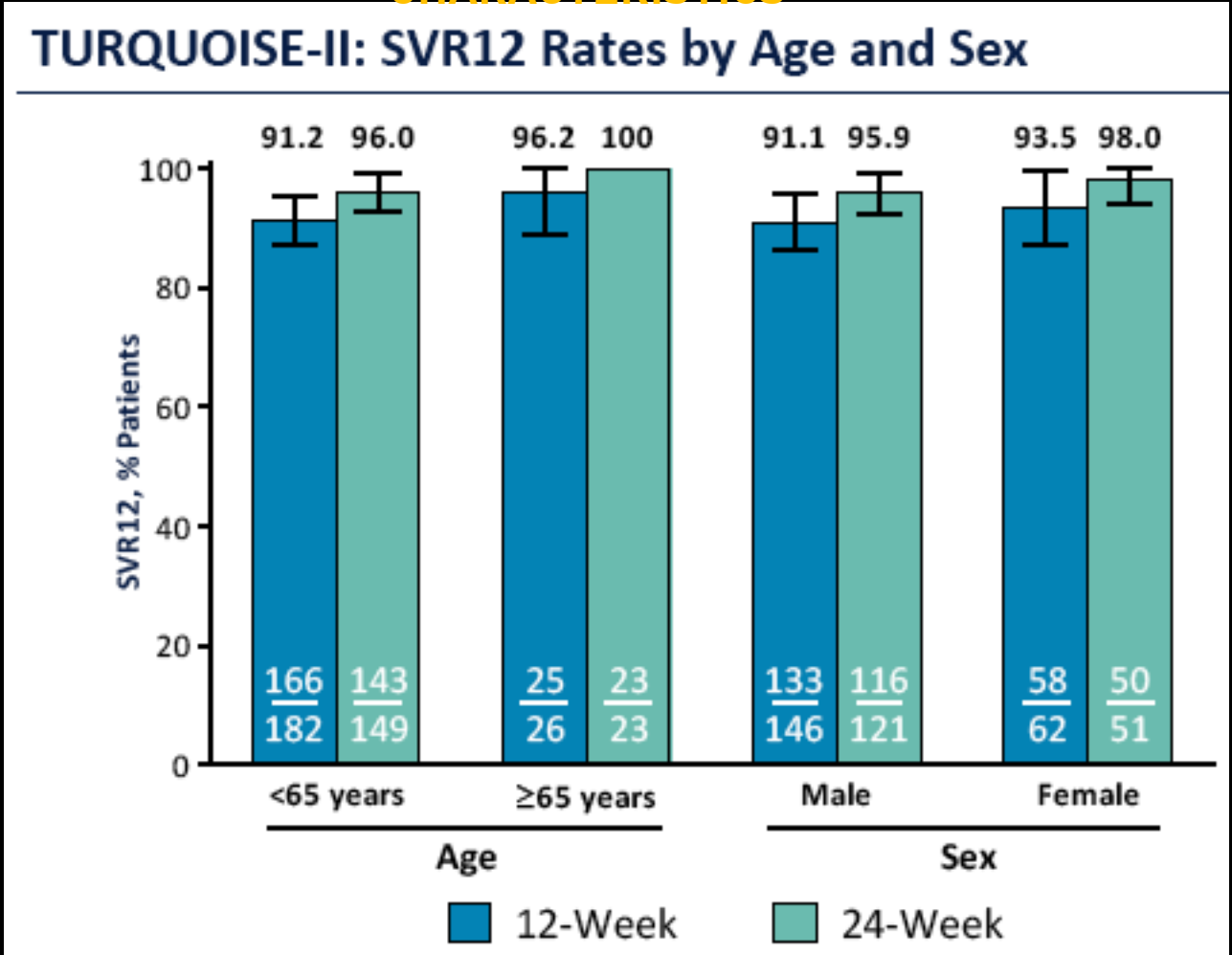

TURQUOISE-II:
SVR12 Rates by BMI and History of Diabetes
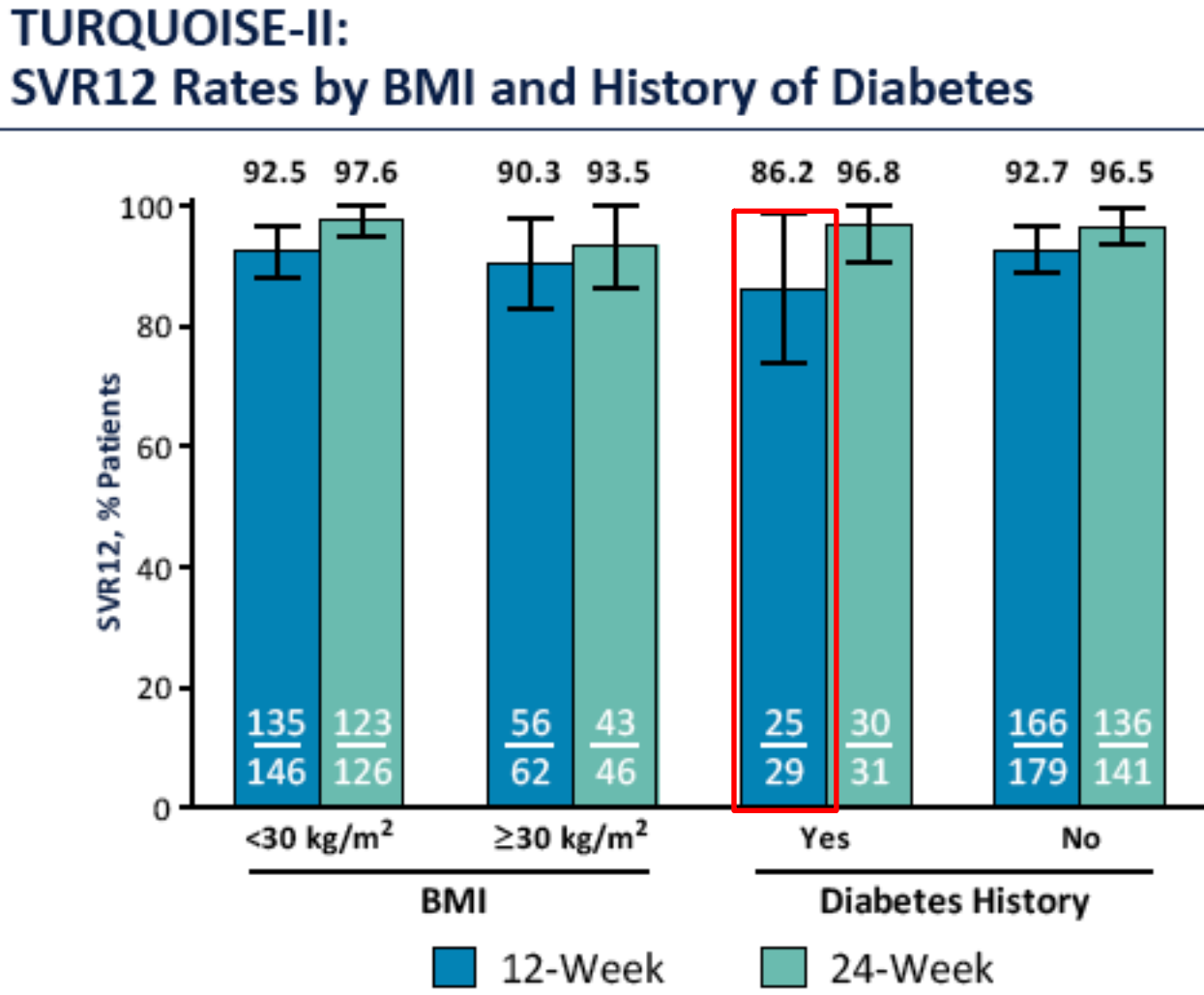
Optimal management of patients with chronic hepatitis C and comorbidities in the era of IFN-FREE all-Oral DAA's

Key points

- Does SVR impact in improving comorbidities?

Effect of antiviral treatment on evolution of liver steatosis in patients with chronic HCV infection: indirect evidence of a role of HCV G3 in steatosis
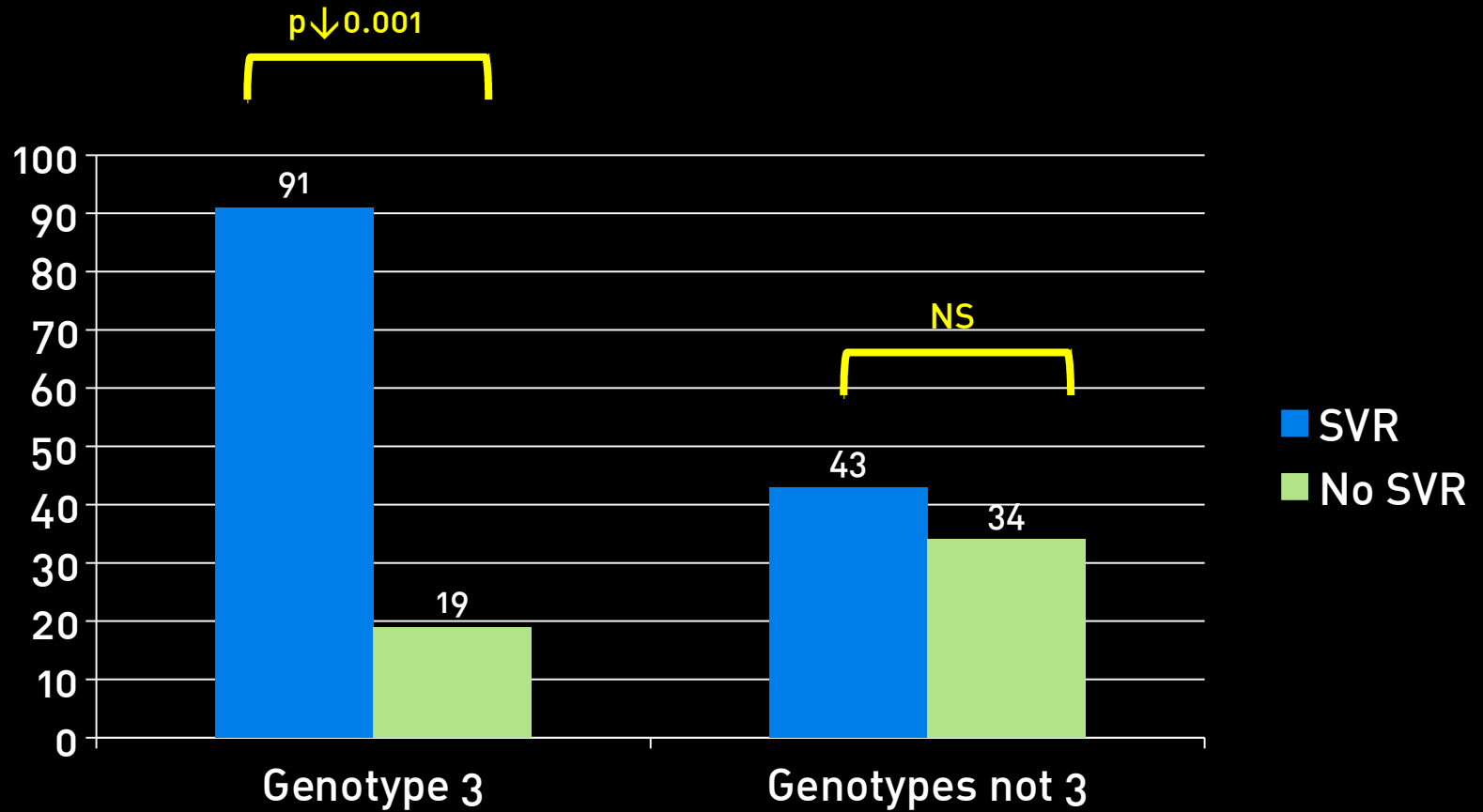
Castera L, et al. Gut 2004

RESPONSE TO IFN-BASED THERAPY AND LONG TERM EFFECT OF HCV ERADICATION IN PATIENTS WITH MC WITH OR WITHOUT SYMPTOMS: A PROSPECTIVE, CONTROLLED, OPEN-LABEL, LONG TERM, COHORT STUDY

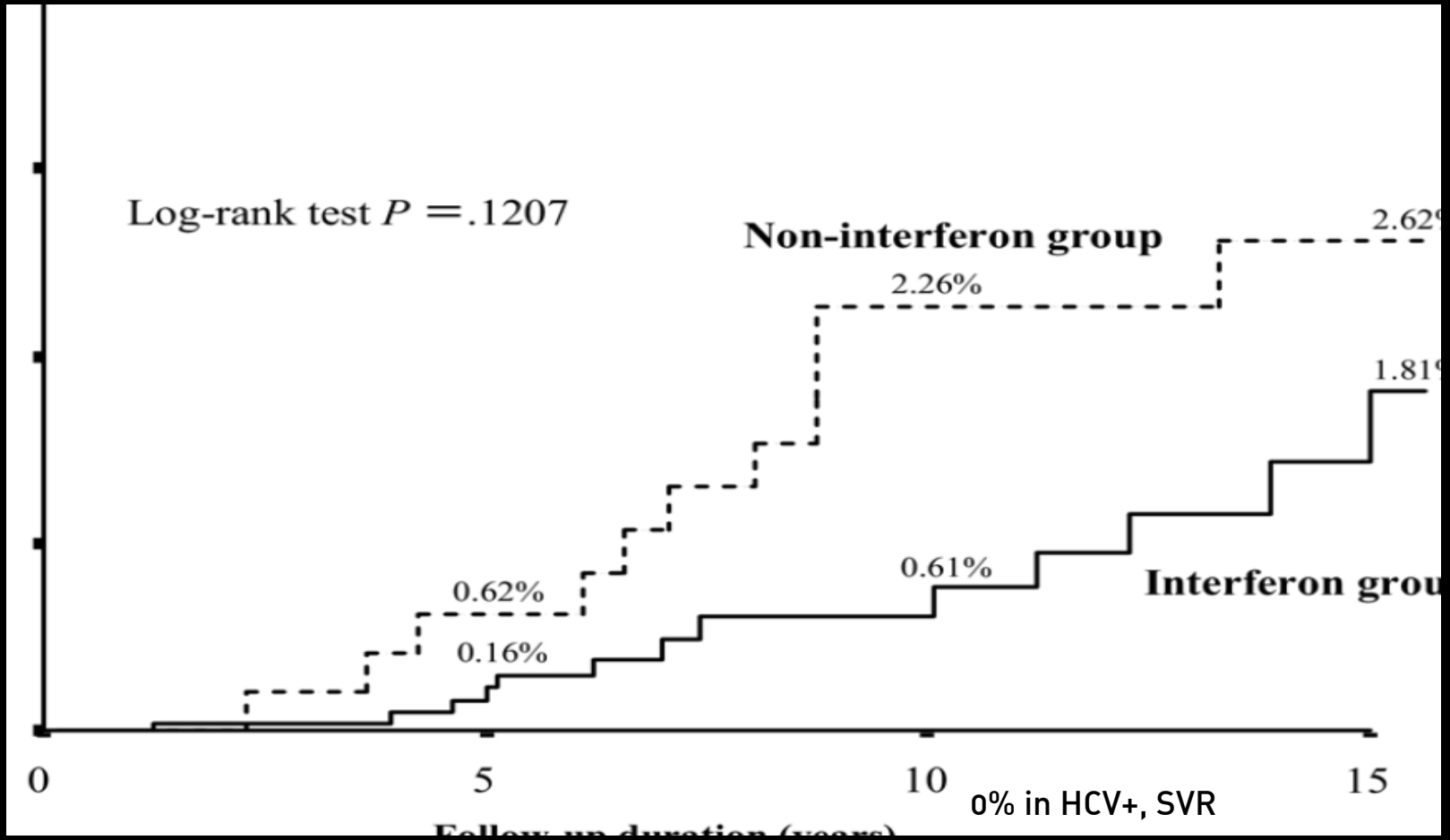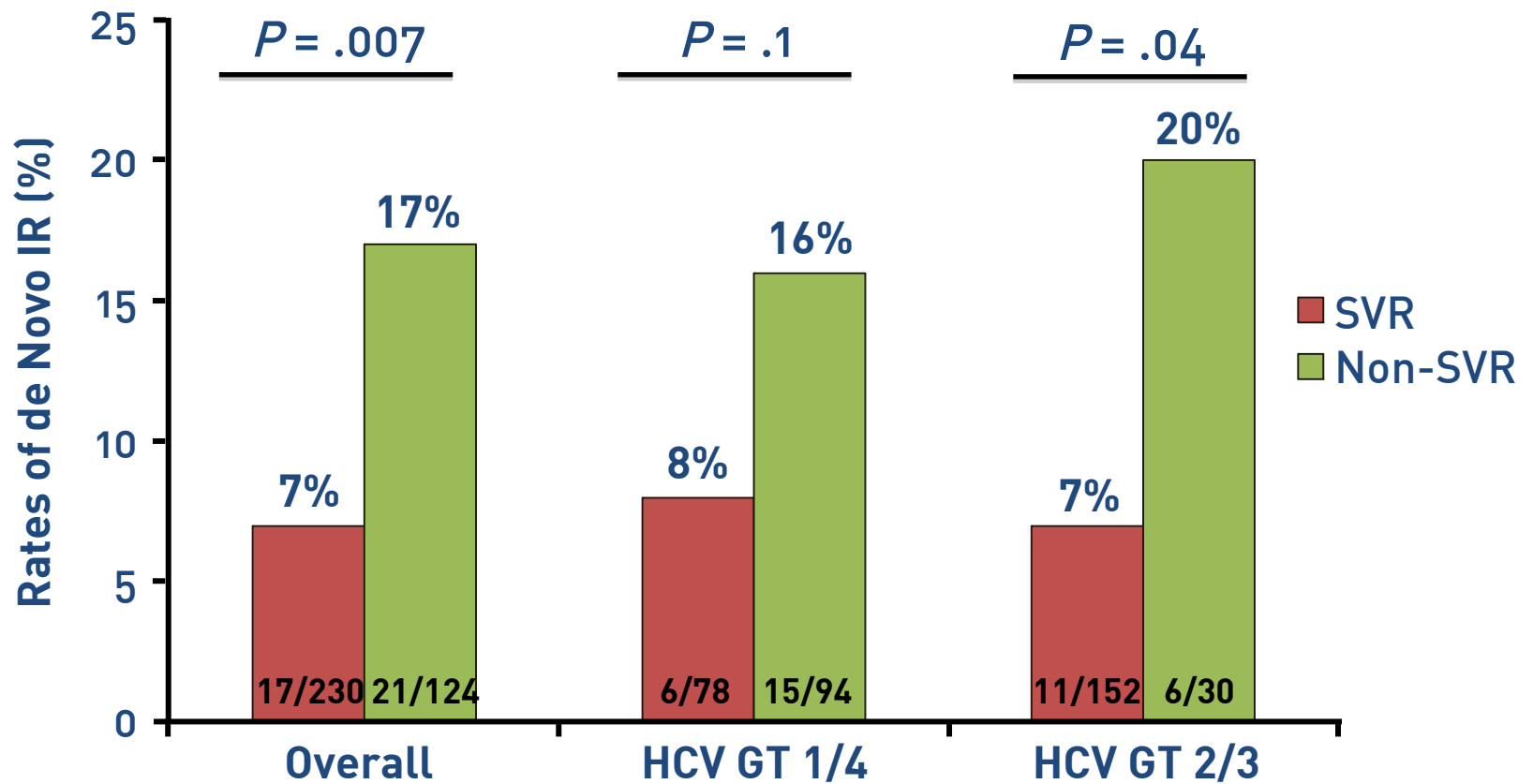**Long-term outcome of HCV MC after antiviral therapy (Peg-IFN+RBV)**

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HCV ELIMINATION REDUCES INCIDENCE OF LYMPHOMA IN PATIENTS WITH HEPATITIS C

Log-rank test $P = .1207$

Non-interferon group — 2.62%

2.26%

1.81%

0.62%

0.16%

0.61%

Interferon group

0% in HCV+, SVR

Follow-up duration (years)

SVR Prevents Development of Insulin Resistance

Aghemo A, et al. Hepatology 2012

Antiviral therapy reduces the complications of diabetes in chronic hepatitis C

Antiviral treatment was associated with a decreased incidence of:

- **End-stage nephropathy (HR 0.16, 95% CI 0.07 – 0.33)**

- **Ischemic stroke (HR 0.53, 95% CI 0.30 – 0.93)**

Hsu CS, et al. Hepatology 2014

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

**Antiviral treatment decreased this risk by ~60%**

Take home message

Optimal management of patients with chronic hepatitis C and comorbidities in the era of IFN-FREE all-Oral DAA's

Key points

- Will wide-spread use of treatment in patients with severe comorbidities impact on overall survival?

SVR by IFN-based therapy was associated with a reduction of all-cause mortality
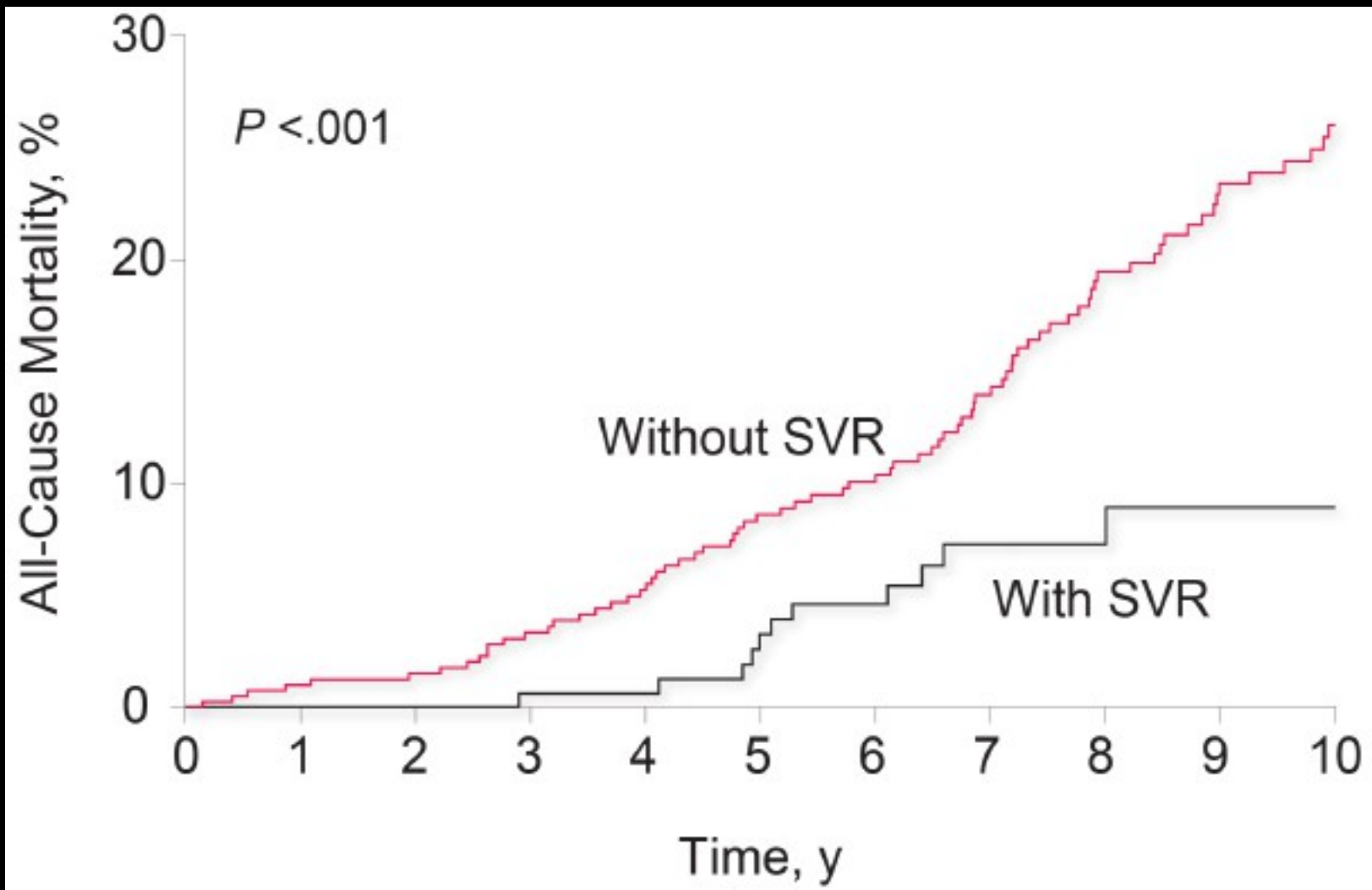
Urgent Treatment With SOF-Based Regimen for Genotype 1 Patients With Severe Renal Insufficiency (GFR ←30ml/min)

Urgency & Treatment Results

	Age	Gender	HCV Gt	Agents	HD	Urgency	Outcome
Patient 1	54	M	1a	Sof 400mg every other day + sim 150 daily	Y	Pre-transplant with normal hepatic synthetic function	SVR 12
Patient 2	64	M	1b	Sof 400mg every other day + sim 150 daily	Y	Pre-transplant with normal hepatic synthetic function	Relapse
Patient 3	62	M	1a	Sof 400 daily + Riba 200 every other day	Y	FCH post LT	SVR 24
Patient 4	53	M	1b	Sof 400mg every other day + sim 150 daily	N	Intense immunosuppression post LKTx	SVR 12

Results

- All patients had "on-treatment response & no viral break throughs

- 3/4 Patients achieved SVR 12.

- The patient with FCH has attained SVR 24. His hepatic function normalized and his GFR also improved significantly to 55ml/min without the need for further dialysis at the end of treatment.

- None had drug discontinuation or SAE.

- Patient 4 was hospitalized during treatment for issues not related to HCV treatment (met with a MVA, plasmapheresis, Immunosuppression and complication after kidney biopsy).

- No deaths occurred even in the FCH patient.

Bhamidimarri KR, et al. AASLD 2014

Should anti-viral treatment be extended to subjects with _older age and /or severe extra-hepatic comorbidities_ since both conditions compete for mortality in patients with HCV- liver disease?
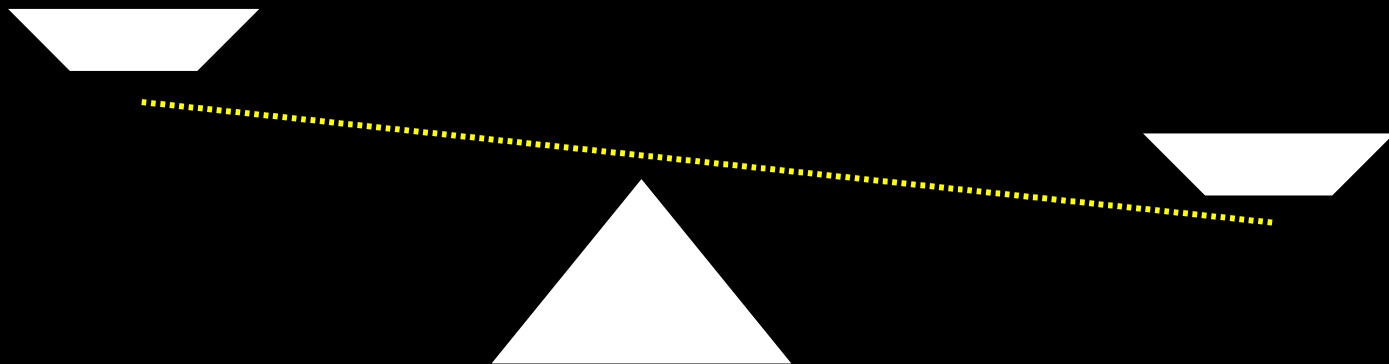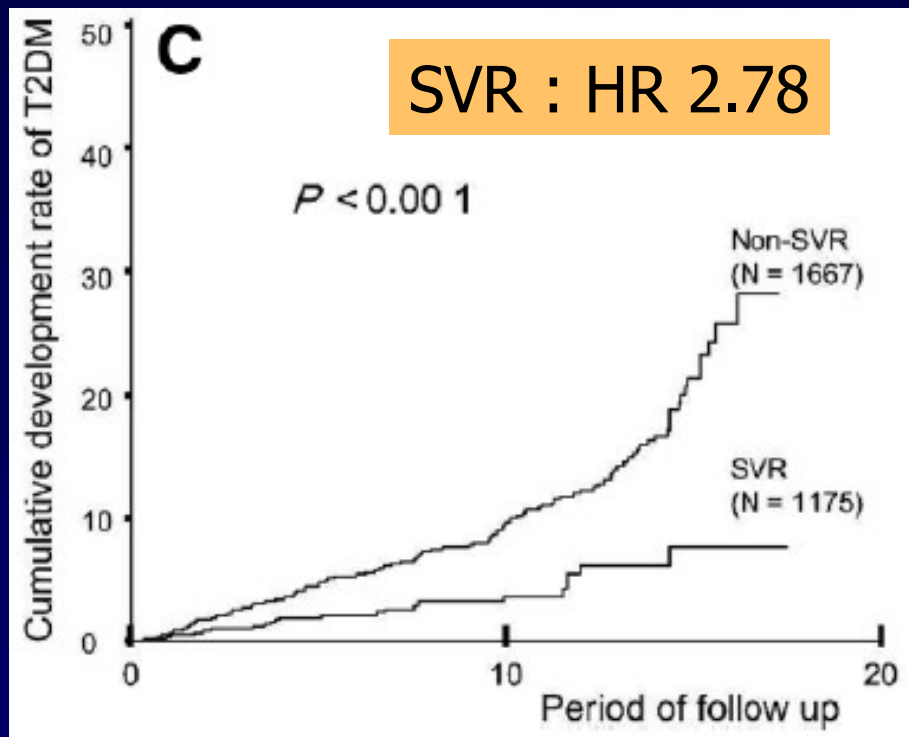
Should anti-viral treatment be extended to subjects with _older age and /or severe extra-hepatic comorbidities_ since both conditions compete for mortality in patients with HCV- liver disease?

Thank you for your attention!

Independent predictors of diabetes

2842 patients with chronic hepatitis C treated IFN or IFN+Ribavirin
F/u 6.4 years

SVR : HR 2.78

Age >50 : HR 2.1

Cirrhosis : HR 3.3

Prediabetes : HR 2.19

What happens after viral eradication /(control) ?

- Fibrosis and cirrhosis may regress … *except* in obese or diabetic patients

- HCC may occur (even in non-cirrhotic patients) … *often when* diabetes/obesity coexist

Marcellin, Lancet 2012
D'Ambrosio, Hepatology 2013
Simonetti, Hepatology 2010

Modifiable factors:
Genotype

Association Between HCV Genotypes (1-4) and Risk of Incident HCC in Subgroup Analyses

Defined Subgroup	Adjusted Hazard Ratio* (95% Confidence Interval)
Patients with cirrhosis (n — 21,716)	
1	1.0
2	0.62 (0.50, 0.77)
3	1.44 (1.23, 1.68)
4	0.96 (0.96, 1.22)
Younger patients (50 years and younger) (n — 55,424)	
1	1.0
2	0.34 (0.24, 0.46)
3	1.86 (1.56, 2.22)
4	1.21 (0.71, 2.05)
Older patients (older than 50 years) (n — 54,898)	
1	1.0
2	0.65 (0.55, 0.76)
3	1.79 (1.53, 2.11)
4	0.81 (0.47, 1.40)
White (n — 57,970)	
1	1.0
2	0.59 (0.49, 0.70)
3	1.93 (1.68, 2.21)
4	1.66 (1.07, 2.56)
African American (n — 36,693)	
1	1.0
2	0.44 (0.26, 0.73)
3	1.23 (0.67, 2.37)
4	0.40 (0.05, 1.00)
Patients without diabetes (n — 98,143)	
1	1.0
2	0.55 (0.47, 0.64)
3	1.87 (1.65, 2.12)
4	1.13 (0.76, 1.67)
Patients with diabetes (n — 12,179)	
1	1.0
2	0.54 (0.36, 0.80)
3	1.30 (1.88, 1.90)
4	0.38 (0.09, 1.53)

Kanwal F, et al. Hepatology 2014

Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3

Thompson AJ, et al. Gut 2012