TRATTARE IL PAZIENTE CON FIBROSI LIEVE:
RISCHI E OPPORTUNITA'

Prof. Gloria Taliani
Dott. Elisa Biliotti
Sapienza Università di Roma

Milano 2 Ottobre 2015
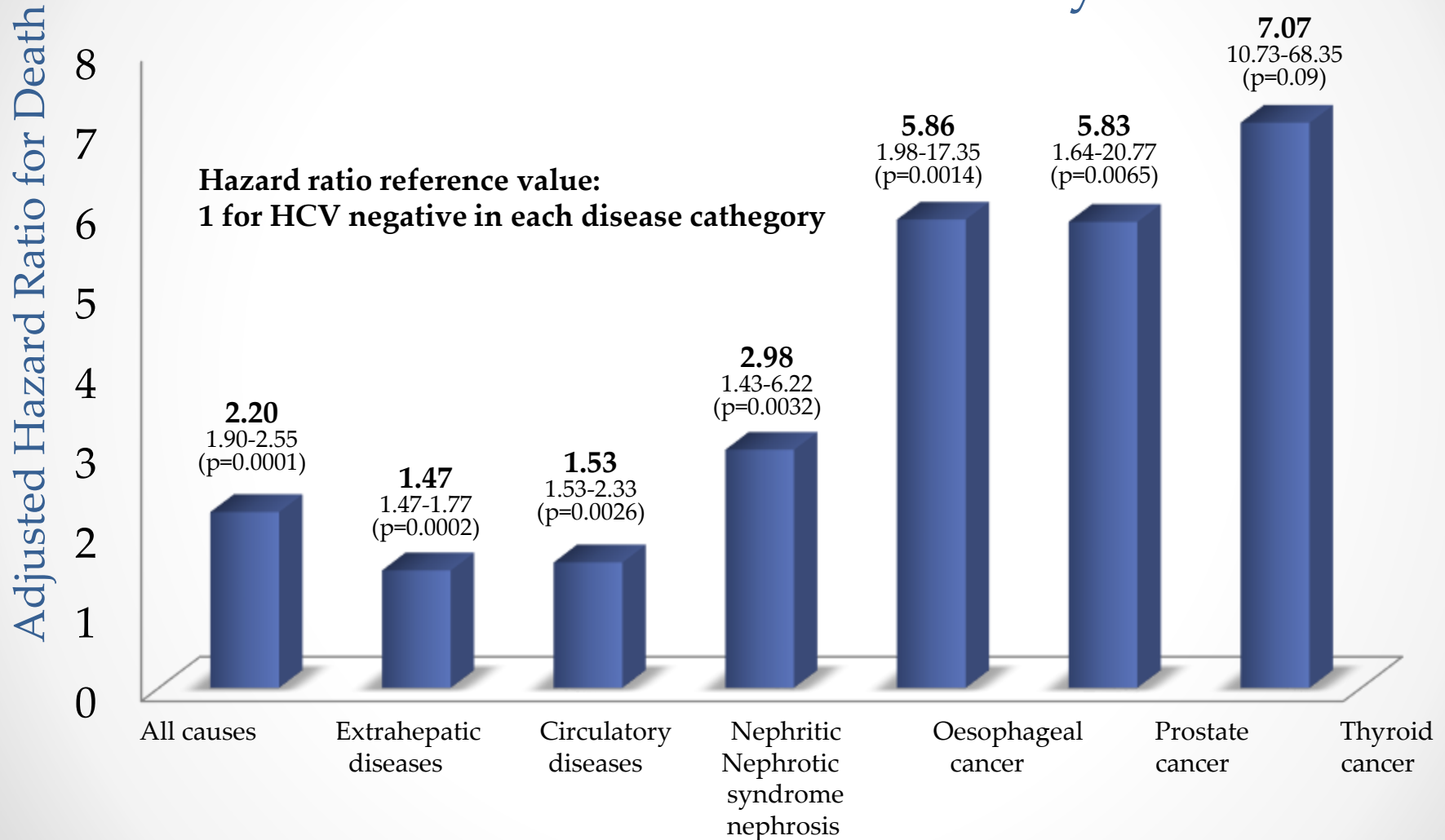
Hepatitis C

- Not only a liver disease

- What HCV "cure" means.....

- Treatment options

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

Is HCV more than a liver disease? Increased mortality "beyond" the liver
The REVEAL cohort study

Adjusted Hazard Ratio for Death

Hazard ratio reference value:
1 for HCV negative in each disease cathegory

2.20
1.90-2.55
(p=0.0001)

1.47
1.47-1.77
(p=0.0002)

1.53
1.53-2.33
(p=0.0026)

2.98
1.43-6.22
(p=0.0032)

5.86
1.98-17.35
(p=0.0014)

5.83
1.64-20.77
(p=0.0065)

7.07
10.73-68.35
(p=0.09)

All causes | Extrahepatic diseases | Circulatory diseases | Nephritic Nephrotic syndrome nephrosis | Oesophageal cancer | Prostate cancer | Thyroid cancer

Multivariable logistic regression analysis of renal cell carcinoma risk factors (prospective study) compared to Colon cancer

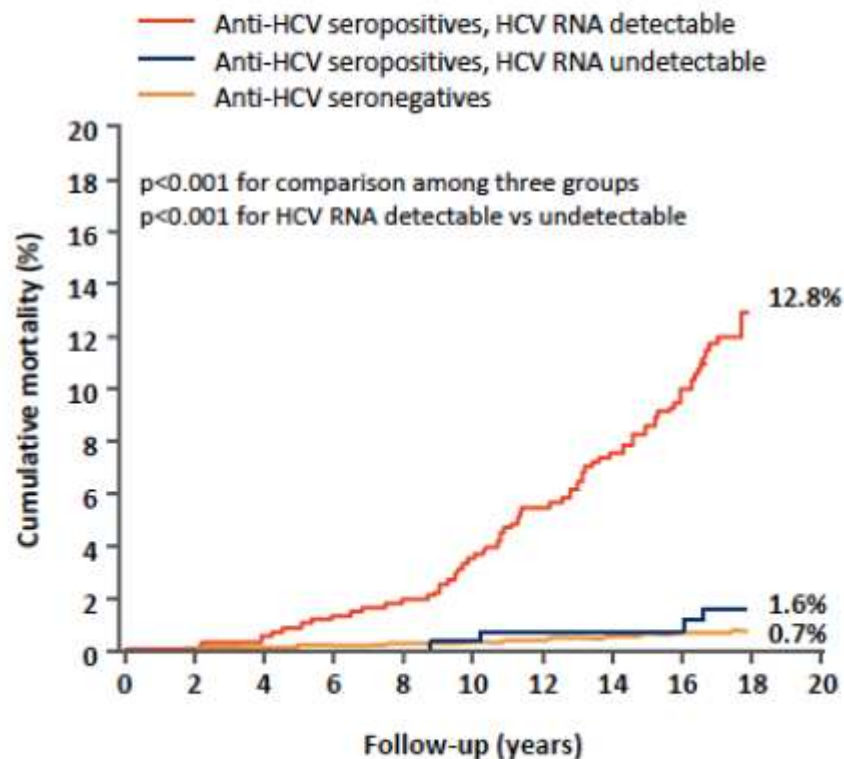|	Odds ratio (95 % confidence limits)	p value
HCV RNA	24.20 (2.4, >999.9)	0.043
Male	0.52 (0.5, 1.7)	0.85
African-American	0.25 (0.3, 0.8)	0.012
Age	0.96 (0.9, 1.0)	0.011
BMI	0.96 (0.7, 1.4)	0.81
Smoking	0.85 (0.5, 1.5)	0.58
Alcohol abuse	0.41 (0.2, 1.0)	0.070
Hypertension	2.48 (1.3, 4.9)	0.008
Diabetes mellitus	0.64 (0.3, 1.3)	0.20
Dyslipidemia	1.58 (0.9, 2.9)	0.16
Coronary artery disease	0.93 (0.4, 2.2)	0.87
Congestive heart failure	0.75 (0.2, 3.0)	0.68
Chronic kidney disease	3.71 (1.2, 15.1)	0.042
Cirrhosis	0.79 (0.2, 9.4)	0.79

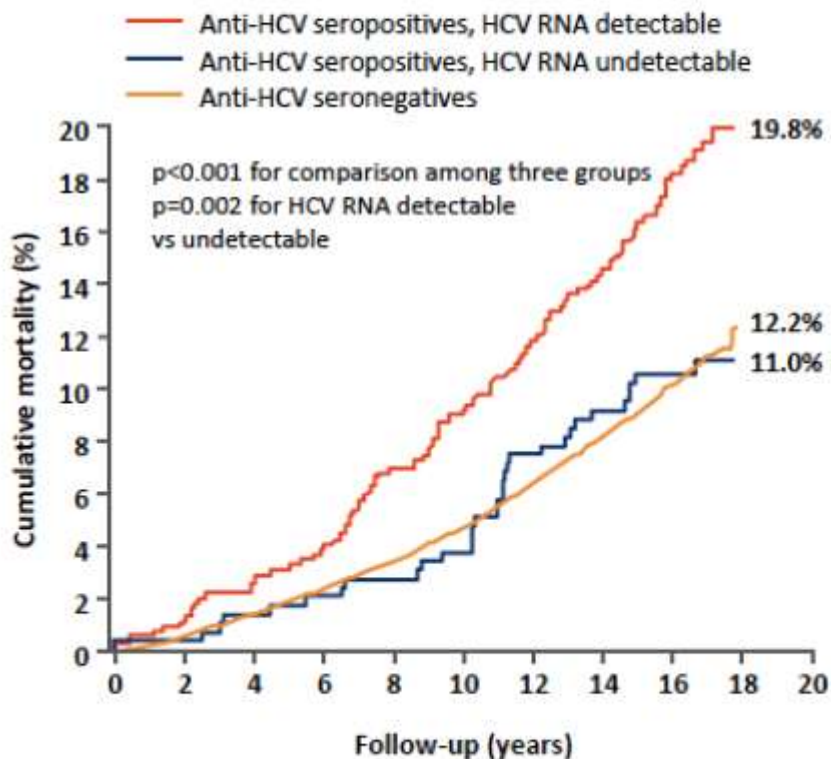# Chronic HCV increases mortality from hepatic and non-hepatic diseases
The REVEAL HCV Cohort Study

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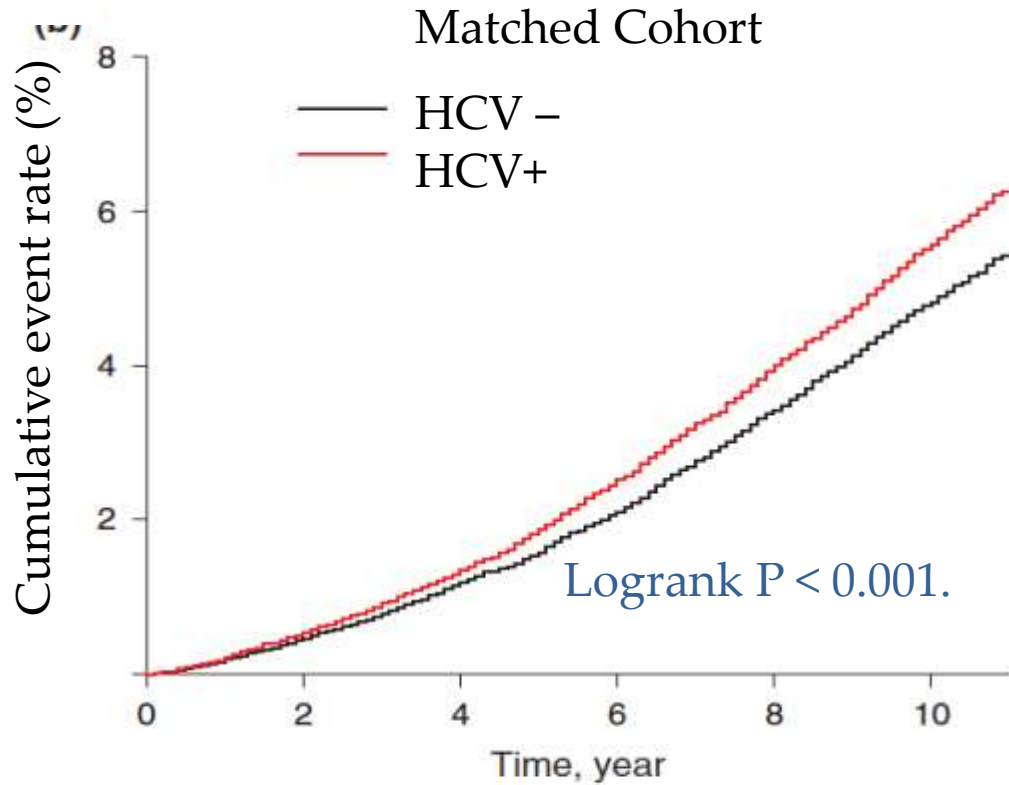- 1095 were anti-HCV positive; 69.4% had detectable HCV RNA

Hepatic diseases

- Anti-HCV seropositives, HCV RNA detectable
- Anti-HCV seropositives, HCV RNA undetectable
- Anti-HCV seronegatives

p<0.001 for comparison among three groups
p<0.001 for HCV RNA detectable vs undetectable

Cumulative mortality (%)

12.8%
1.6%
0.7%

Follow-up (years)

Extrahepatic diseases

- Anti-HCV seropositives, HCV RNA detectable
- Anti-HCV seropositives, HCV RNA undetectable
- Anti-HCV seronegatives

p<0.001 for comparison among three groups
p=0.002 for HCV RNA detectable vs undetectable

Cumulative mortality (%)

19.8%
12.2%
11.0%

Follow-up (years)

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

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

Matched Cohort

58.570 pairs of HCV-infected and HCV non-infected, matched with a 1:1 ratio by:

sex, age, income, urbanization, diabetes, Hypertension, hypercholesterolemia, chronic obstructive pulmonary disease and depressive disorder.

Logrank P < 0.001.

No. at risk						
HCV(+)	58 525	56 525	53 436	49 522	42 931	36 298|
HCV(−)	58 525	56 525	53 436	49 522	42 931	36 298

Chiu WC et al. European J Neurology 2014: 21:1068

# Emotional Intelligence single component scores according to HCV status
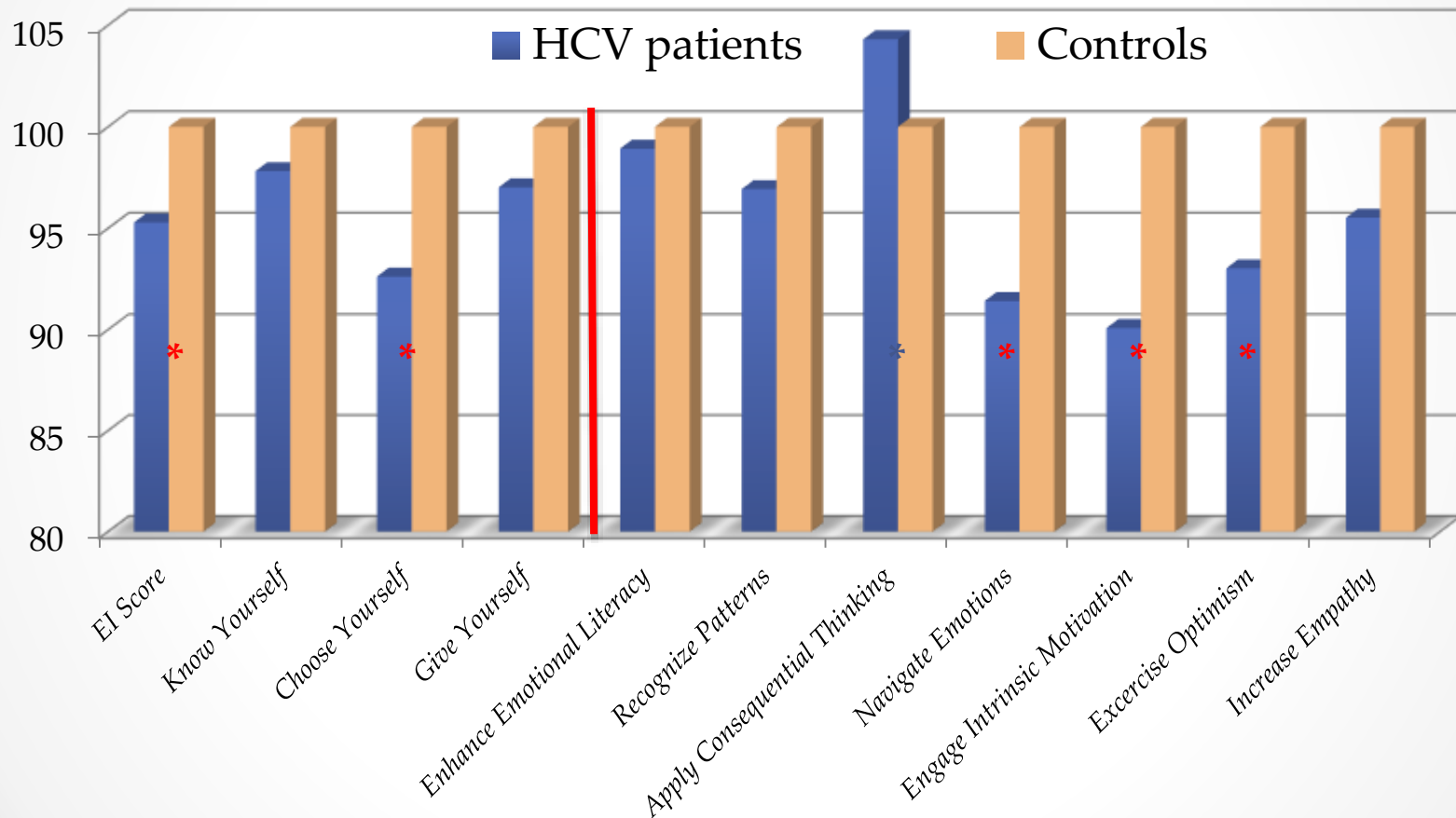
Concerns about Studies on Fibrosis progression

Conclusions regarding the natural history of HCV infection are difficult to draw from these studies, given
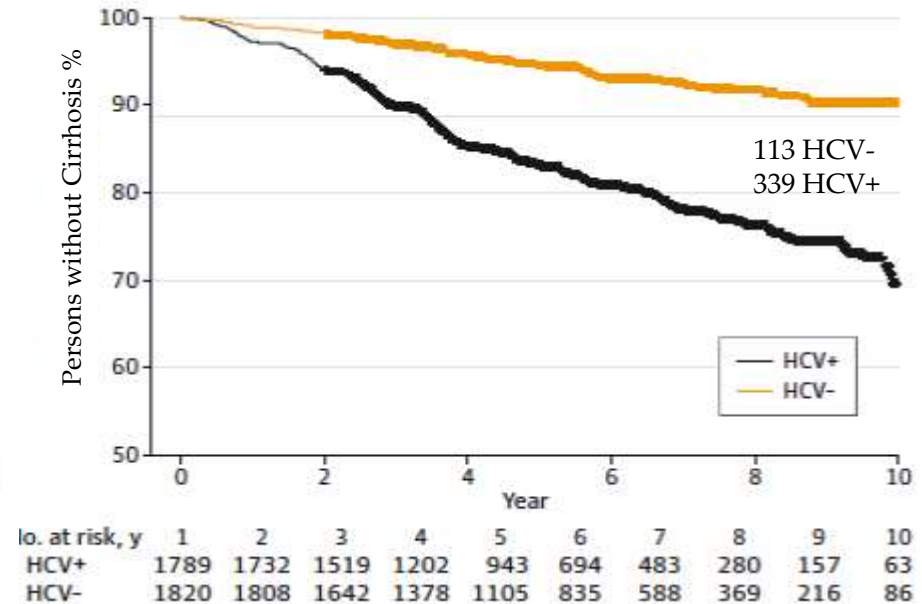
- The retrospective design
- The heterogeneity of study populations
- **Inherent selection bias (patients unwilling to undergo liver biopsies were excluded)**

Progression of Liver Fibrosis Over Time and Kaplan-Meier Curves of Time to FIB-4 Increase and Cirrhosis Development
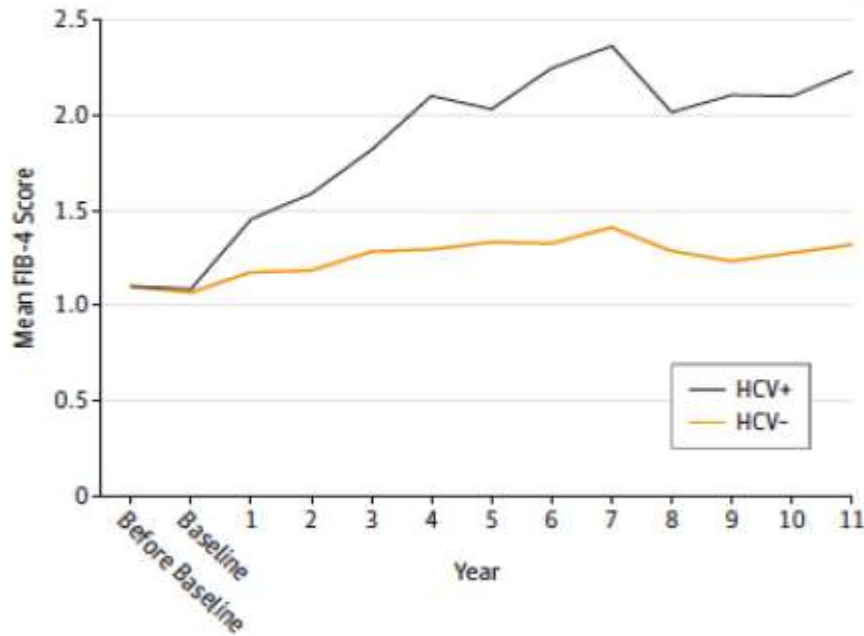
Higher risk of cirrhosis:

HCV+: increasing age, white race, hypertension, history of alcohol abuse, anemia.

HCV-: alcohol abuse and anemia

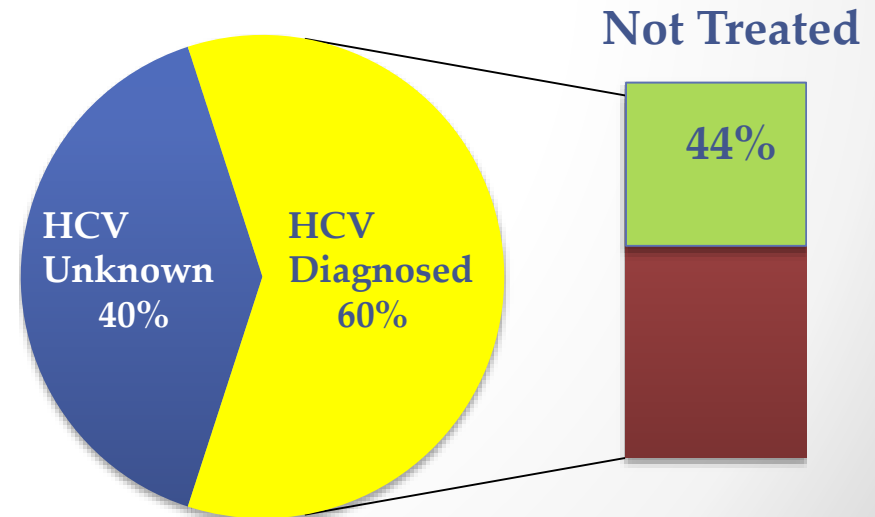*Butt AA et al. JAMA Intern Med. 2015;175(2):178-185.*

Most patients with HCV-associated lymphoma present with mild liver disease: a call to revise antiviral treatment prioritization

89 patients with HCV-NHL.
Genotype 1 (62%),
Diffuse large B cell lymphomas (62%)
Detectable HCV RNA (90%) at NHL diagnosis.

Advanced liver disease (Metavir stage ≥ 3) in only 18% of the patients at the time of HCV-NHL diagnosis.
In 53 patients chronic HCV infection documented before lymphoma diagnosis

AVT not recommend in 44%,

Not Treated

44%

HCV Unknown 40%

HCV Diagnosed 60%

Torres HA et al. Liver Int. 2015; 35: 1661–1664

Most patients with HCV-associated lymphoma present with mild liver disease: a call to revise antiviral treatment prioritization

89 patients with HCV-NHL.
Genotype 1 (62%),
Diffuse large B cell lymphomas (62%)
Detectable HCV RNA (90%) at NHL diagnosis.

Advanced liver disease (Metavir stage ≥ 3) in only 18% of the patients at the time of HCV-NHL diagnosis.
In 53 patients chronic HCV infection documented before lymphoma diagnosis

AVT not recommend in 44%,

Because of the lack of advanced liver disease at HCV diagnosis: 38%

Not Treated

44%

HCV Unknown 40%

HCV Diagnosed 60%

Torres HA et al. Liver Int. 2015; 35: 1661–1664
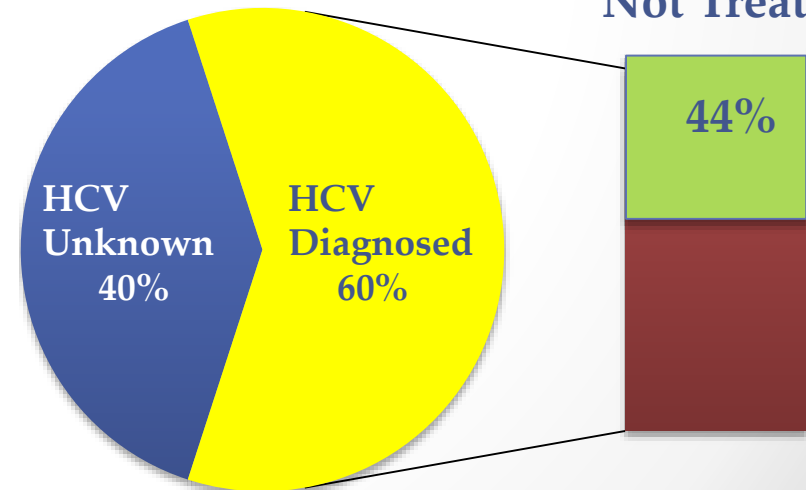
Hepatitis C

- Not only a liver disease

- What HCV "cure" means…..

- Treatment options

Factors Associated With Increased Risk Of Secondary Outcomes In Patients With HCV

Characteristic	Cirrhosis	HCC	Liver related Hospitalization
	(n=123,988)	(n=128,481)	
Male gender	1.35 (1.21–1.50)	3.41 (2.39–4.88)	1.09 (1.01-1.17)
Age	1.02 (1.02–1.02)	1.07 (1.07–1.07)	0.99 (0.99-0.99)
Race White	1 (reference)	1 (reference)	1 (reference)
Black	0.54 (0.52–0.56)	0.73 (0.68–0.78)	0.74 (0.72-0.76)
Other	0.73 (0.70–0.76)	0.80 (0.74–0.87)	0.58 (0.56-0.60)
HCV genotype			
1	1 (reference)	1 (reference)	1 (reference)
2	0.64 (0.61–0.68)	0.52 (0.46–0.58)	0.80 (0.76-0.83)
3	1.24 (1.18–1.31)	1.63 (1.47–1.79)	1.10 (1.05-1.15)
Other	0.87 (0.75–1.00)	0.77 (0.57–1.04)	0.89 (0.79-0.99)
Diabetes	1.38 (1.32–1.44)	1.31 (1.21–1.42)	1.19 (1.15-1.24)
Undetectable HCV-RNA	0.62 (0.54–0.73)	0.62 (0.42–0.81)	0.71 (0.63-0.80)

Factors Associated With Increased Risk Of Secondary Outcomes In Patients With HCV

Characteristic	Cirrhosis	HCC	Liver related Hospitalization
	(n=123,988)	(n=128,481)	
Male gender	1.35 (1.21–1.50)	3.41 (2.39–4.88)	1.09 (1.01-1.17)
Age	1.02 (1.02–1.02)	1.07 (1.07–1.07)	0.99 (0.99-0.99)
Race White	1 (reference)	1 (reference)	1 (reference)
Black	0.54 (0.52–0.56)	0.73 (0.68–0.78)	0.74 (0.72-0.76)
Other	0.73 (0.70–0.76)	0.80 (0.74–0.87)	0.58 (0.56-0.60)
HCV genotype			
1	1 (reference)	1 (reference)	1 (reference)
2	0.64 (0.61–0.68)	0.52 (0.46–0.58)	0.80 (0.76-0.83)
3	1.24 (1.18–1.31)	1.63 (1.47–1.79)	1.10 (1.05-1.15)
Other	0.87 (0.75–1.00)	0.77 (0.57–1.04)	0.89 (0.79-0.99)
Diabetes	1.38 (1.32–1.44)	1.31 (1.21–1.42)	1.19 (1.15-1.24)
Undetectable HCV-RNA	0.62 (0.54–0.73)	0.62 (0.42–0.81)	0.71 (0.63-0.80)

# Factors Associated With Increased Risk Of Secondary Outcomes In Patients With HCV

| Characteristic	Cirrhosis	HCC	...
	(n=123,988)		
Male gender	1.35 (1.3...		
Age			
Ra...			
HCV			
1		1 (reference)	1 (reference)
2		0.52 (0.46–0.58)	0.80 (0.76-0.83)
3	...31)	1.63 (1.47–1.79)	1.10 (1.05-1.15)
Other	...7 (0.75–1.00)	0.77 (0.57–1.04)	0.89 (0.79-0.99)
Diabetes	1.38 (1.32–1.44)	1.31 (1.21–1.42)	1.19 (1.15-1.24)
Undetectable HCV-RNA	0.62 (0.54–0.73)	0.62 (0.42–0.81)	0.71 (0.63-0.80)

Patients who achieve an undetectable viral load **reduce their risk of death by 45%** relative to those patients whose viral load was detectable over the entire period following their diagnosis.

McCombs, JAMA Intern Med 2014;174:204–212

HCV Elimination Reduces The Incidence of Malignant Lymphoma

Kawamura Y, et al. Am J Med 2007;120:1034-1041
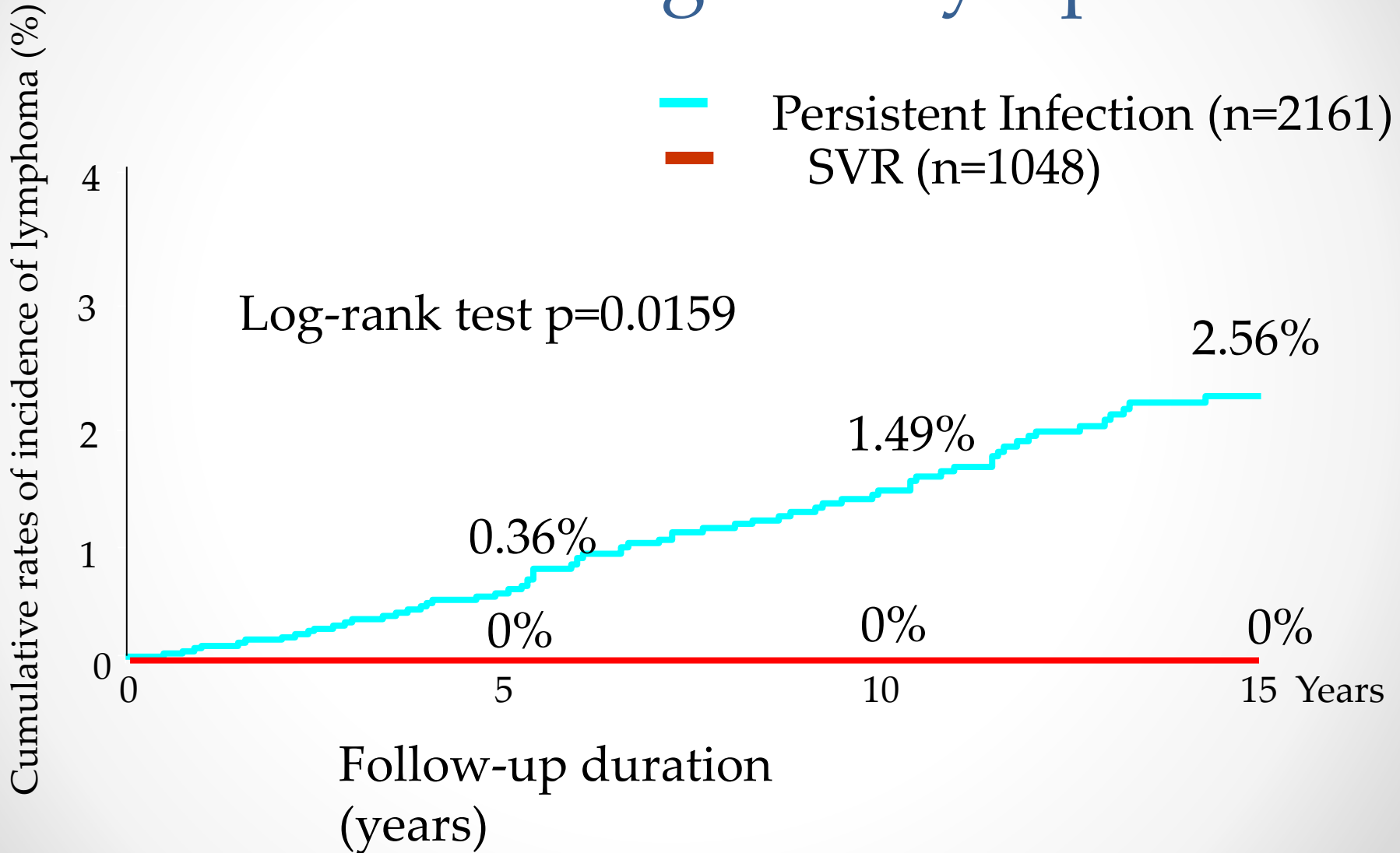
Cumulative incidence of type 2 diabetes in chronic hepatitis C: SVR *vs* non-SVR

Annual incidence of T2D in hepatitis C: 0.8-1.0%
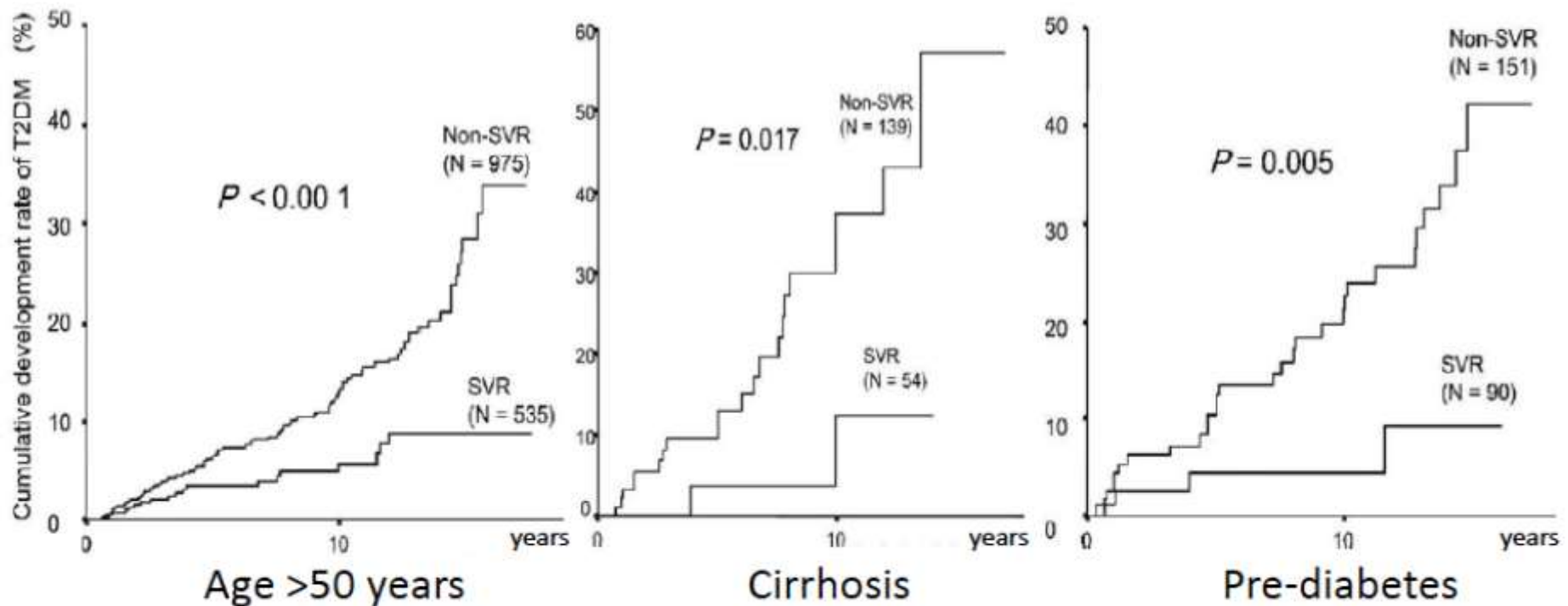
Cure of HCV reduces the risk of developing T2D by more than two thirds

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

HCV and Stroke

The excess risk of Peripheral Artery Disease in HCV-infected patients
1.43 (95% CI = 1.23–1.67)
The risk with any four comorbidities   9.25 (95% CI 0 6.35-13.5)

(hypertension, Diabetes, hyperlipidemia, ischemic herat disease, COPD, chronic kidney disease)

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 HCV + (208 treated)
12.452 uninfected controls Taiwan National Insurance Program Database
HCV infection associated with **23% increase of the risk of stroke** (afer correction for risk factors)
Antiviral treatment decreases this risk by 60%

● *Hsu YH et al. Journal of Hepatology 2015: 62: 519–525*

Cumulative incidence of ischemic stroke, ESRD and acute coronary event in three study cohorts of diabetic patients

Modified log rank test with death adjusted as a competing risk event.
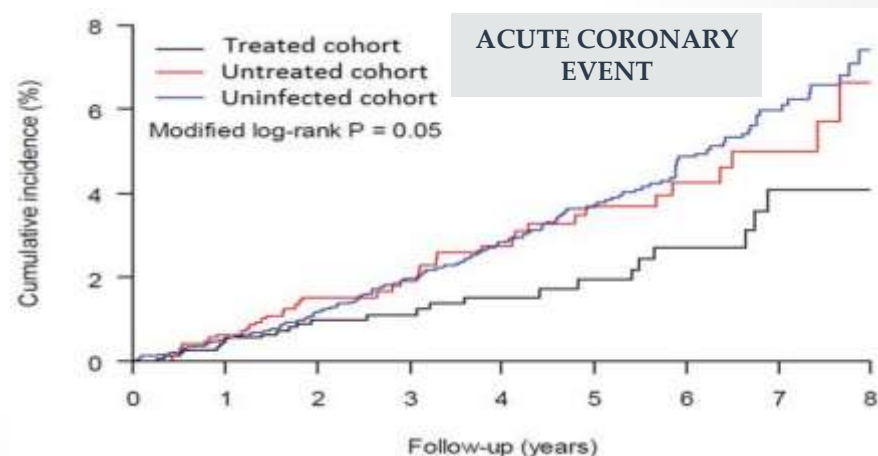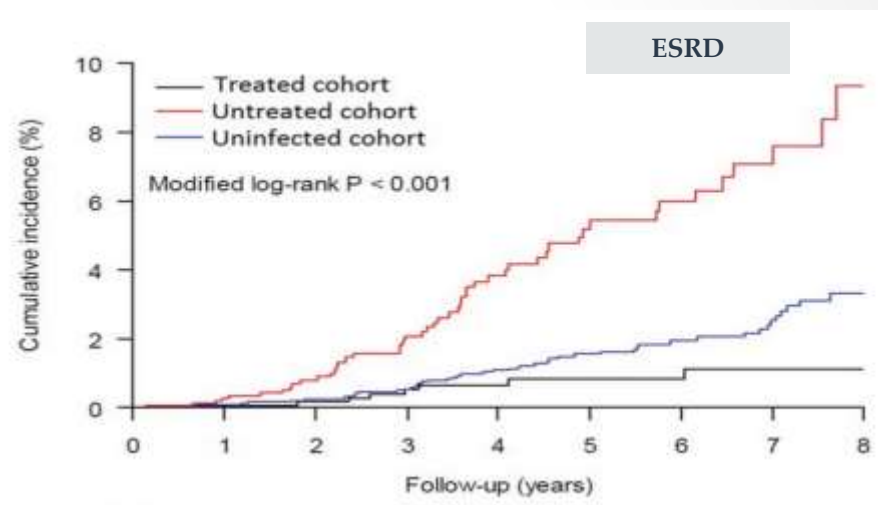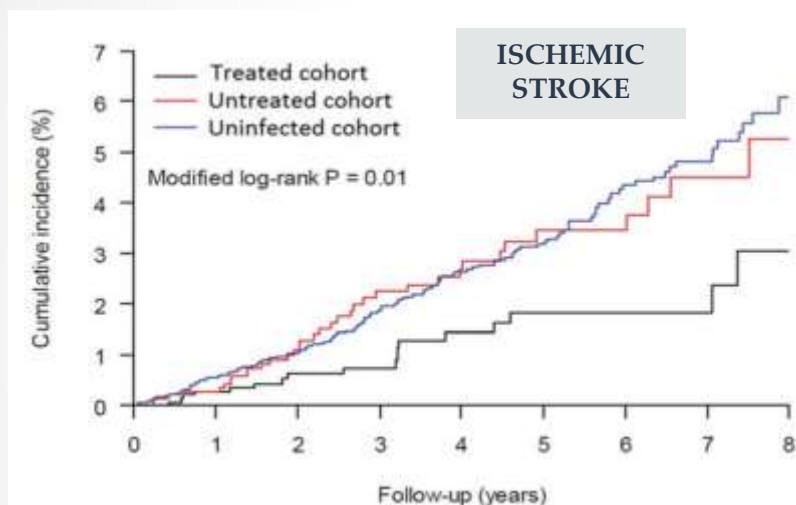
Antiviral therapy for concomitant HCV infection is associated with improved renal and cardiovascular outcomes in patients with DM

Hsu YC et al. HEPATOLOGY 2014;59:1293-1302

SVR is associated with a reduction in all-cause mortality

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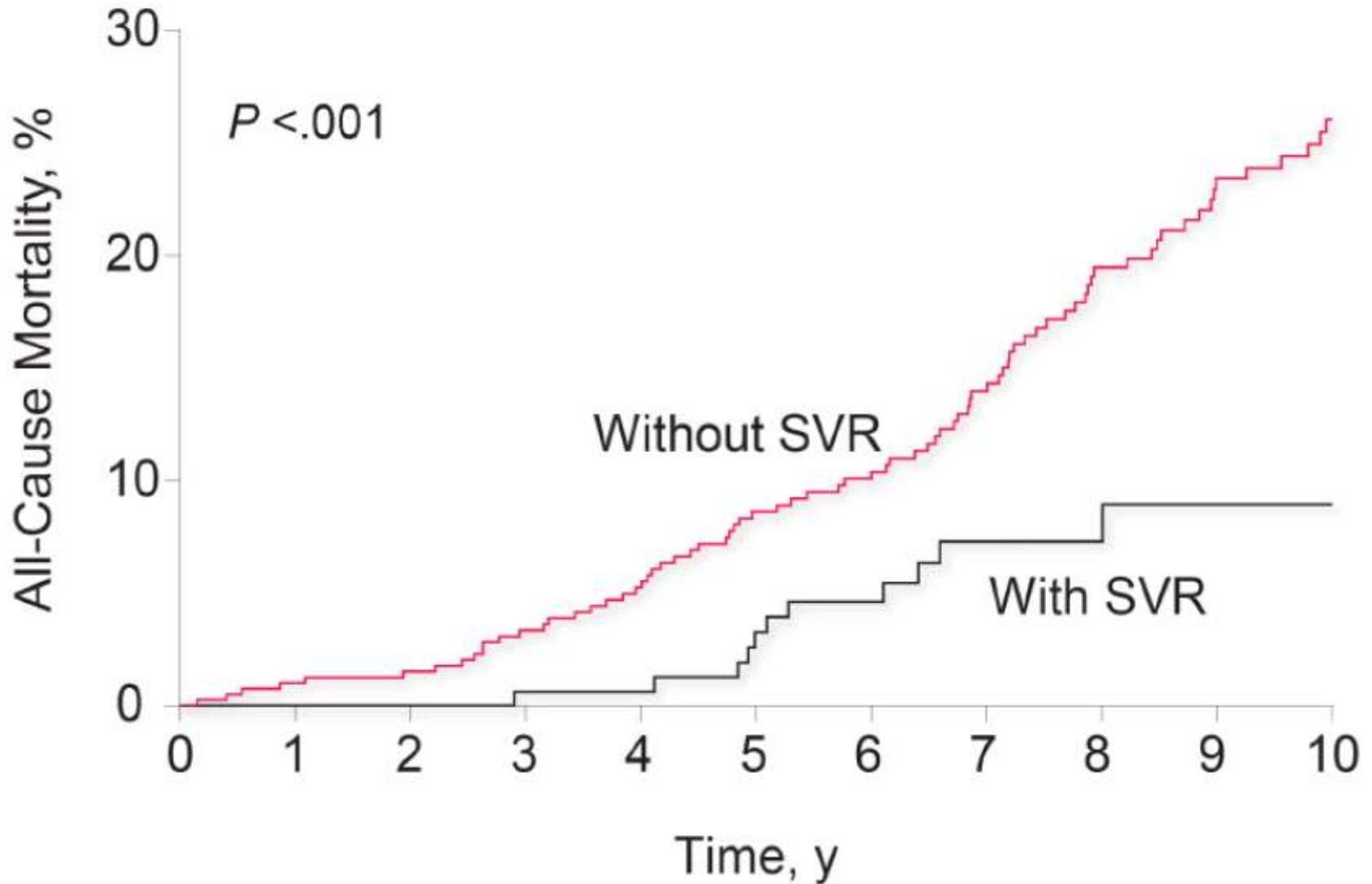
Hepatitis C

- Not only a liver disease

- What HCV "cure" means.....

- Treatment options

EASL Guidelines 2015 and AASLD-IDSA RECOMMENDATIONS

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy **(A1)**

- Treatment should be **prioritized** for patients with significant fibrosis or cirrhosis (METAVIR score F3 to F4) **(A1)**

1. A cost-effective treatment should respect **resource (macro) and individual (micro) allocation criteria**;

2. Patients should be carefully **informed**, particularly on **treatment deferral**

1. criteria for eligibility to treatment should be clearly identified and **updated periodically**;

Sacchini D et al. Dig Liver Dis. 2014

Tipologie di pazienti che hanno accesso al rimborso AIFA

Epatite cronica con fibrosi METAVIR ≥3

Cirrosi in classe di Child A o B e/o con HCC con risposta completa a resezione chirurgica o terapia loco-regionale, non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi

Epatite cronica F≥2 con gravi manifestazioni extra-epatiche HCV-correlate

In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi

Recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR ≥2 o fibrosante colestatica

Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2

Epatite cronica con fibrosi METAVIR F0-2
(solo per Simeprevir in associazione con Peg-R)

Impact of *IL28B* on Treatment Outcome in Hepatitis C Virus G1/4 Patients Receiving Response-Guided Therapy with Peginterferon Alpha-2a (40KD)/Ribavirin

Thomas-Matthias Scherzer,[1] Albert Friedrich Stättermayer,[1] Michael Strasser,[2] Hermann Laferl,[3] Andreas Maieron,[4] Rudolf Stauber,[5] Christian Datz,[6] Emina Dulic-Lakovic,[7] Petra Steindl-Munda,[1] Harald Hofer,[1] and Peter Ferenci[1]

517 treated patients

Patients with an EVR		Patients without an EVR	Patients with an RVR
Group A Peginterferon alfa-2a plus ribavirin x 48 weeks ITT=139 rs12979860 analysis n=93 (67%)	**Group B** Peginterferon alfa-2a plus ribavirin x 72 weeks ITT=150 rs12979860 analysis N=90 (60%)	**Group C** Peginterferon alfa-2a plus ribavirin x 72 weeks ITT=78 rs12979860 analysis N=48 (62%)	**Group D** Peginterferon alfa-2a plus ribavirin x 24 weeks ITT=150 rs12979860 analysis N=97 (65%)
139 (26.9%)	228 (44.1%)		150 (29%)

What do we need….

- The most cost-effective treatment
  - o Short
  - o Effective
  - o Safe

SMV + PR: pooled QUEST 1 and 2* (C208 and C216)

- Randomised, double-blind, Pbo-controlled, Phase III studies investigating the safety and efficacy of SMV 150 mg + PR (NCT01289782 + NCT01290679)

RGT*

Treatment-naïve, HCV genotype 1 patients	pooled n=521	SMV 150 mg QD + PR	PR
			Follow up / PR
	pooled n=264	Pbo + PR	PR / PR

Week 0   12   24   48
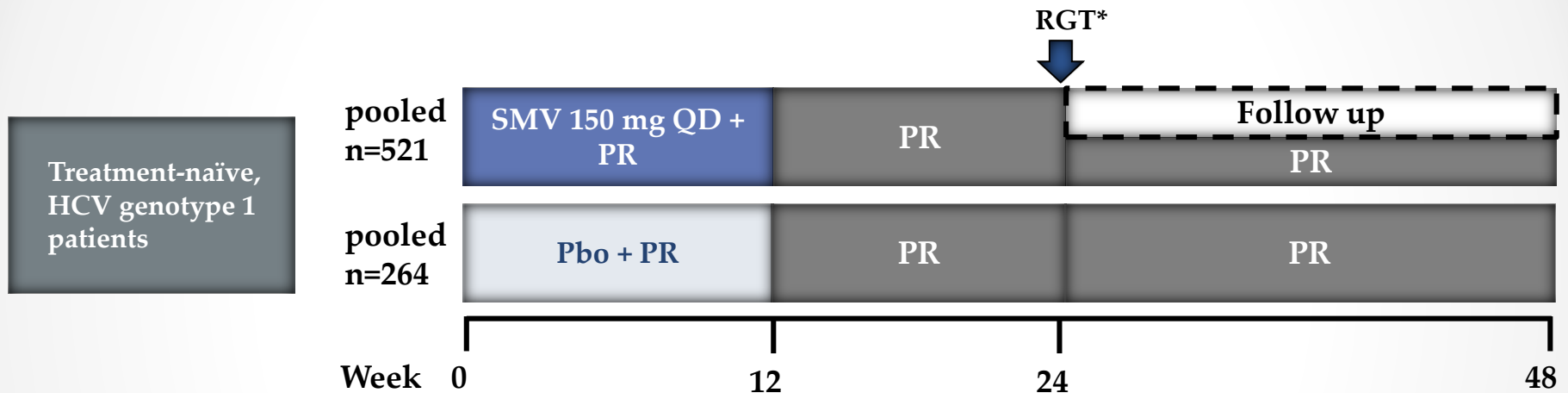
- **RGT:** patients were eligible to stop therapy at Week 24 if HCV RNA <25 IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Week 12

- Patients were stratified by HCV subtype and IL28B genotype

- **Primary endpoint:**
  - SVR 12

*QUEST-1: 30% F3-F4; 56% G1a
QUEST-2: 21% F3-F4, 41% G1a

Jacobson IM et al. Lancet. 2014; 384: 403-13
Manns M et al. Lancet. 2014; 384: 414-26

Pooled QUEST 1 & 2 analysis – SVR12 according to RGT criterion in European patients

Patients treated with SMV + PR

Met RGT criteria , which allowed shortening of treatment

Treatment-naïve and prior **relapser** patients Including 20-30% of **cirrhosis**

91% (252/276) of patients eligible for 24 weeks of treatment

SVR12 (%)

92

231/ 252

SVR12

Foster G, et al. EASL 2014. Poster P1127

Pooled QUEST 1 & 2 analysis – SVR12 according to RGT criterion in European patients

Patients treated with SMV + PR

Treatment-naïve and prior **relapser** patients
Including 20-30% of **cirrhosis**

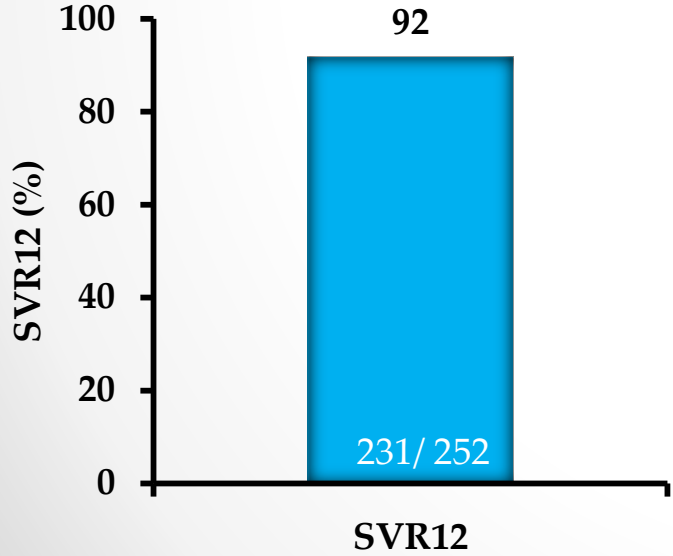**Met RGT criteria , which allowed shortening of treatment**

91% (252/276) of patients eligible for 24 weeks of treatment

Did not meet RGT criteria

7% (18/276) of patients

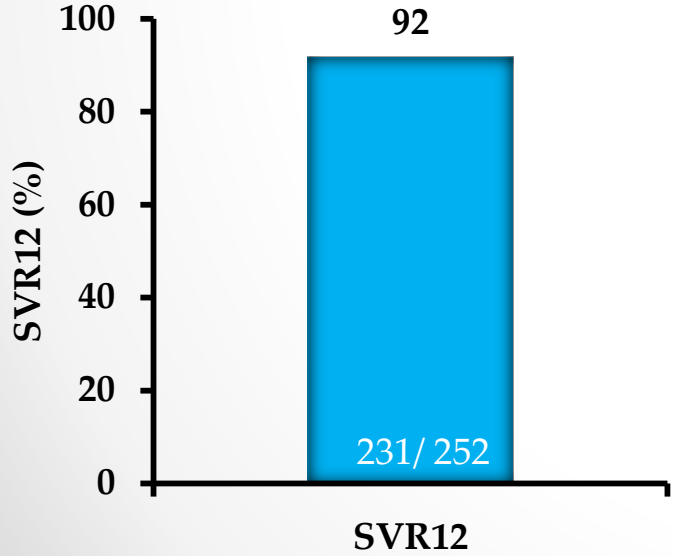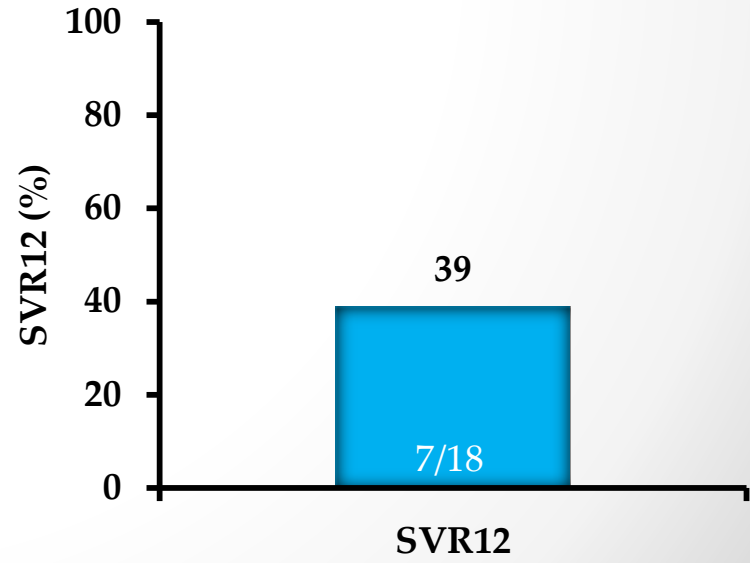RGT criteria: HCV RNA <25 IU/mL, detectable/undetectable at Week 4 and <25IU/mL undetectable at Week 12

SMV + PR: pooled QUEST 1 and 2 – SVR12 in patients with **RVR** by select baseline disease characteristics
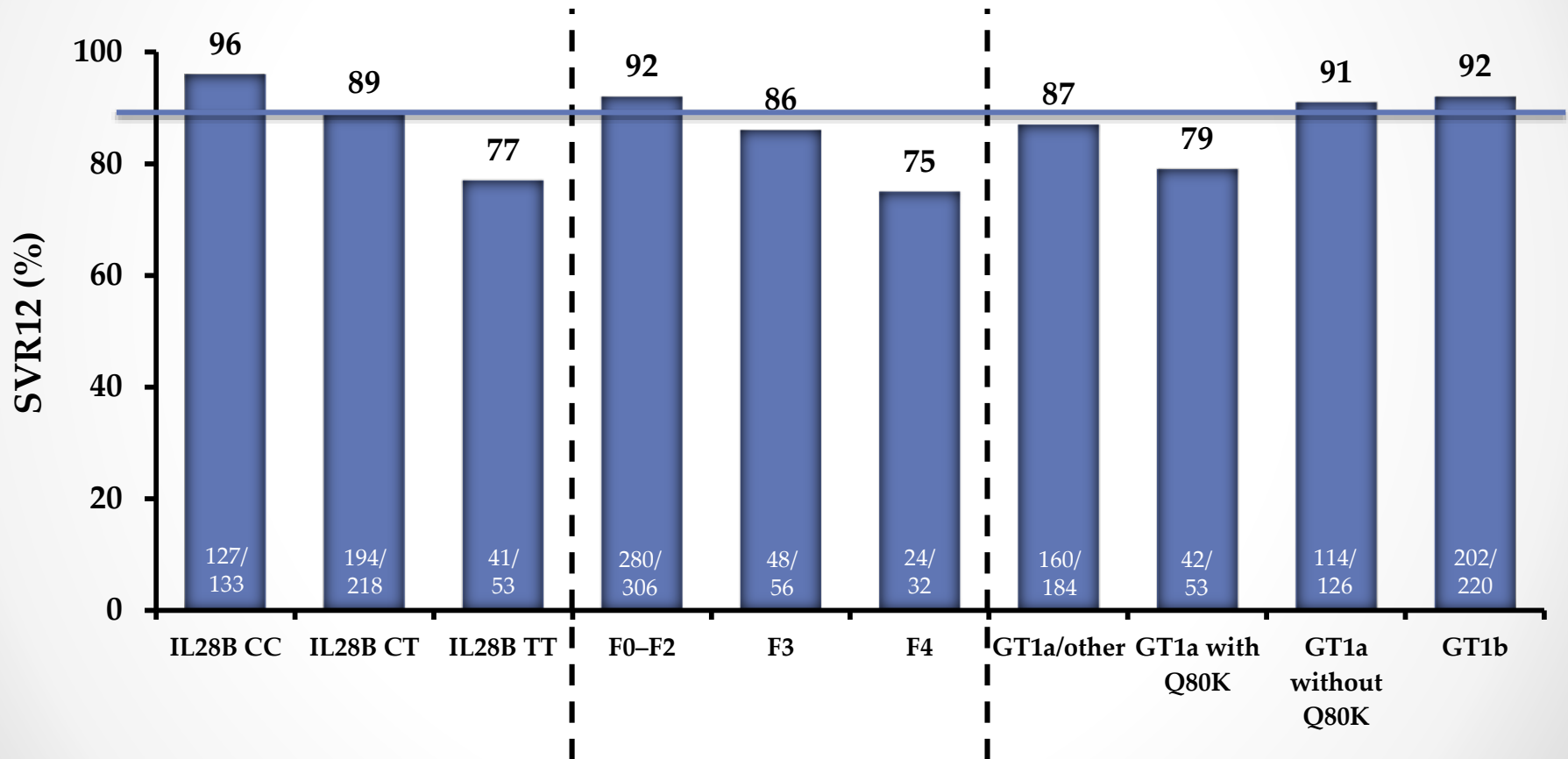
SMV + PR: PROMISE – study design

- Randomised, double-blind, Pbo-controlled, Phase III study investigating the safety and efficacy of SMV 150 mg + PR (NCT01281839)

- **Prior relapse,** HCV genotype 1 patients
- Patients were stratified by HCV subtype and *IL28B* genotype

RGT*

n=260 | SMV 150 mg QD + PR | PR | Follow up / PR †

n=133 | Pbo + PR | PR | PR

Week 0 — 12 — 24 — 48
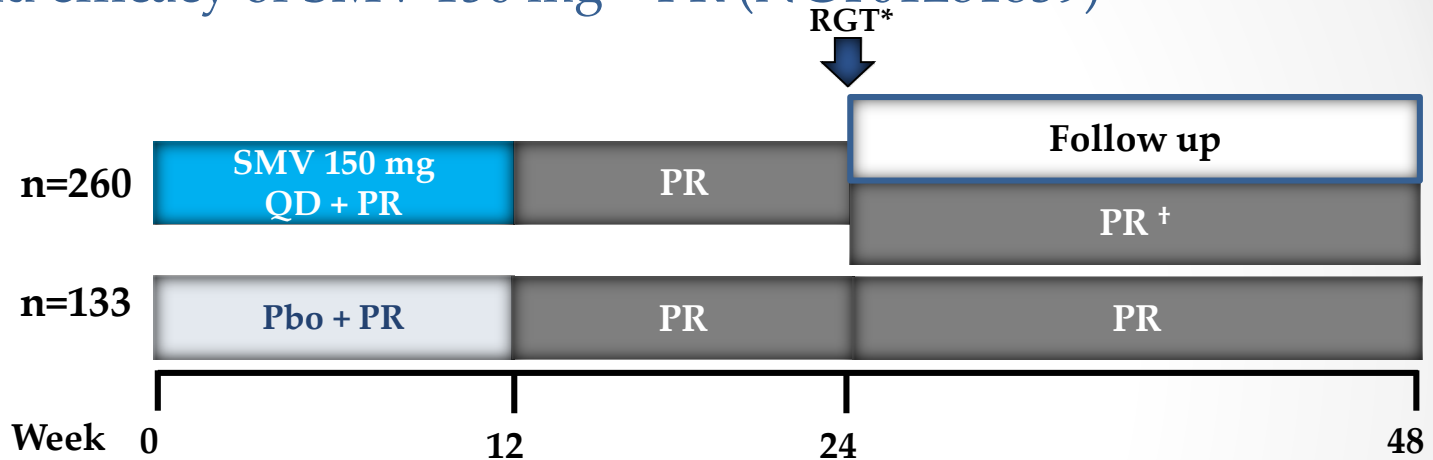
- **Primary endpoint**
  - SVR 12
- **Secondary endpoint**
  - SVR24, safety and tolerability, fatigue severity, limitation in daily activities

F3-F4: 33%
G1a: 42%

*RGT: stop all therapy if HCV RNA <25 IU/mL detectable or undetectable at Week 4 and <25 IU/mL undetectable at Week 12
† patients who did not qualify for RGT were treated with PR until week 48

Forns X, et al. Gastroenterology 2014;146:1669–1679

SMV + PR: PROMISE – SVR in RVR* by fibrosis stage
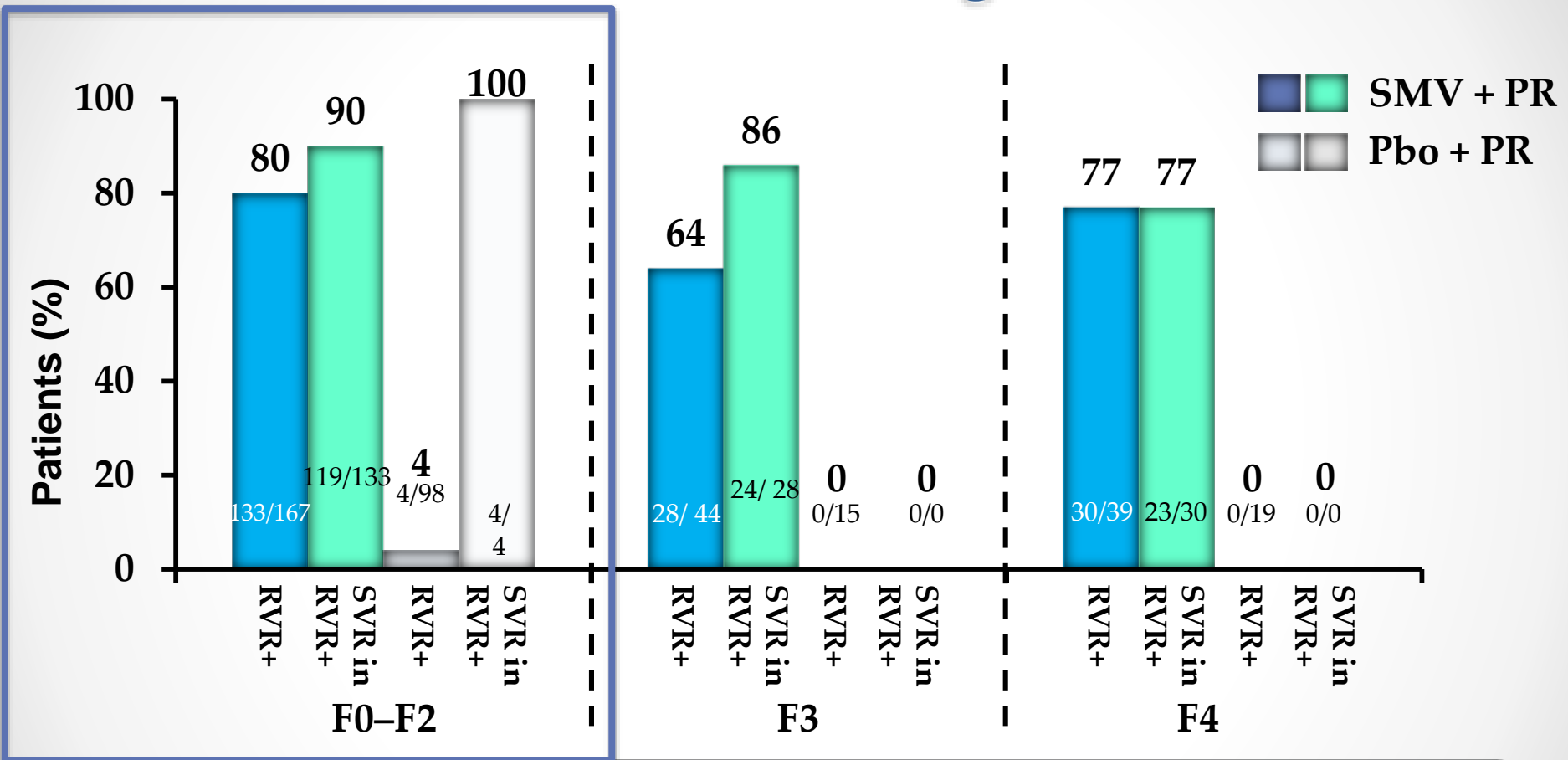
RVR rates were significantly higher with SMV + PR vs Pbo + PR, regardless of fibrosis stage

P<0.001
*RVR defined as undetectable HCV RNA at Week 4
No statistical testing was pre-planned or carried out for these subgroups RVR: rapid virologic response

Forns X et al. Gastroenterology 2014;146:1669–1679

Triple Stop Study: Objectives

- In this Phase III, open-label trial, the efficacy and safety of a **12-week SMV + PR regimen** in treatment-naïve chronic HCV genotype 1-infected patients with a **Week 2** virologic response were investigated[1]

    o The objective of this multivariate analysis was to determine the baseline factors associated with a SVR12 and relapse, and thus to identify patients who may benefit from shorter (12 weeks) SMV + PR therapy

SVR12 = sustained virologic response, 12 weeks after end of treatment

Asselah T, et al. EASL 2015. Poster P0792

Triple Stop Study: **Design**

- European multicentre, open-label, single-arm, Phase III clinical trial

- **HCV GT1**
- **Naïve, F0-F2**
- **All IL28B genotypes**

SMV + PR

Follow-up

PR

Follow-up

12-week group

24-week group*

weeks   0 2   12   24   36   48

*Patients in France had the option to extend to 48 weeks: 1 patient
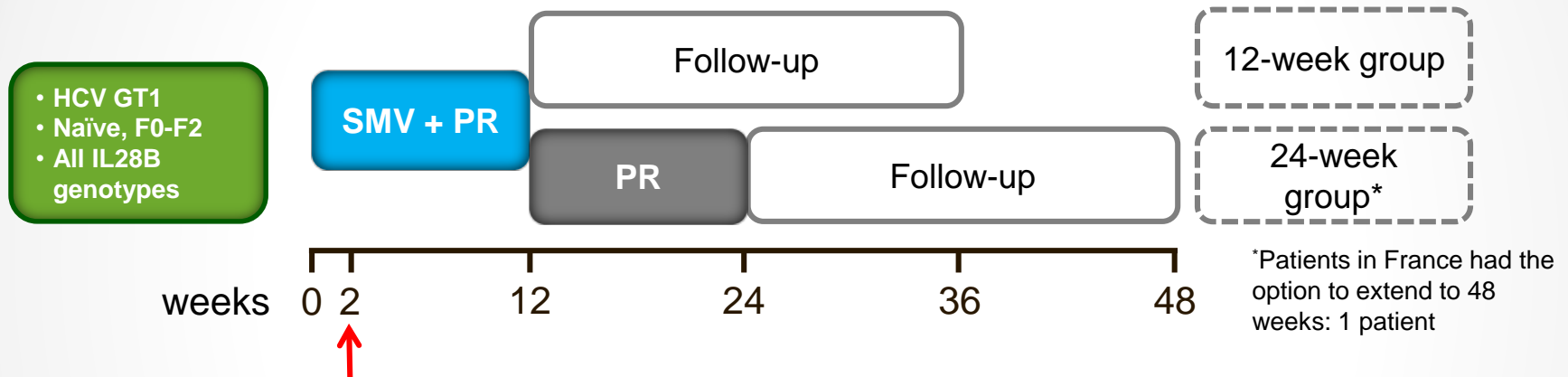
Week 2: qualification for 12 week treatment

Treatment Algorithm		
IL28B genotype	**HCV RNA at Week 2 of treatment**	**Treatment duration**
All	<25 IU/mL undetectable	12 weeks*
	<25 IU/mL detectable	
	≥25 IU/mL detectable	24 weeks

*To qualify for 12 weeks patients must also have HCV RNA <25 IU/mL undetectable at Week 4 and Week 8
Patients stopped all therapy if HCV RNA ≥25 IU/mL at Week 4
Roche COBAS® Taqman® lower limit of quantification: 25 IU/mL, limit of detection: 15 IU/mL   Asselah T, et al. EASL 2015. Poster P0792

Triple Stop Study: Classification and Regression Tree Analysis: Full Analysis

Overall SVR

Observed	Predicted
66% (81/123)	66%

IL28B CC SVR

Observed	Predicted
94% (30/33)	93%

IL28B non-CC SVR

Observed	Predicted
56% (51/91)	56%

Baseline viral load <6,510,000 IU/mL SVR

Observed	Predicted
87% (14/16)	86%

Baseline viral load ≥6,510,000 IU/mL SVR*

Observed	Predicted
100% (16/16)	98%

METAVIR F0–F1

Observed	Predicted
67% (46/69)	67%

METAVIR F2

Observed	Predicted
23% (5/22)	25%

METAVIR F0–F1

Observed	Predicted
91% (10/11)	89%

METAVIR F2

Observed	Predicted
80% (4/5)	78%

Baseline viral load <2,400,000 IU/mL SVR

Observed	Predicted
50% (5/10)	51%

Baseline viral load ≥2,400,000 IU/mL SVR

Observed	Predicted
0% (0/12)	0%

Baseline viral load <1,020,000 IU/mL SVR

Observed	Predicted
89% (24/27)	88%

Baseline viral load ≥1,020,000 IU/mL SVR

Observed	Predicted
52% (22/42)	53%

*Of these 16 patients, 13 were F0–F1, two were F2 and one was unknown

Asselah T, et al. EASL 2015. Poster P0792

Triple Stop Study: Classification and Regression Tree Analysis: Full Analysis

Overall SVR

Observed	Predicted
66% (81/123)	66%

IL28B CC SVR

Observed	Predicted
94% (30/33)	93%

IL28B non-CC SVR

Observed	Predicted
56% (51/91)	56%

Baseline viral load <6,510,000 IU/mL SVR

Observed	Predicted
87% (14/16)	86%

Baseline viral load ≥6,510,000 IU/mL SVR*

Observed	Predicted
100% (16/16)	98%

METAVIR F0–F1

Observed	Predicted
67% (46/69)	67%

METAVIR F2

Observed	Predicted
23% (5/22)	25%

METAVIR F0–F1

Observed	Predicted
91% (10/11)	89%

METAVIR F2

Observed	Predicted
80% (4/5)	78%

Baseline viral load <2,400,000 IU/mL SVR

Observed	Predicted
50% (5/10)	51%

Baseline viral load ≥2,400,000 IU/mL SVR

Observed	Predicted
0% (0/12)	0%

Baseline viral load <1,020,000 IU/mL SVR

Observed	Predicted
89% (24/27)	88%

Baseline viral load ≥1,020,000 IU/mL SVR

Observed	Predicted
52% (22/42)	53%

*Of these 16 patients, 13 were F0–F1, two were F2 and one was unknown

Triple Stop Study: **Subgroups with Predicted SVR > 90%**

Asselah T, et al. EASL 2015. Poster P0792
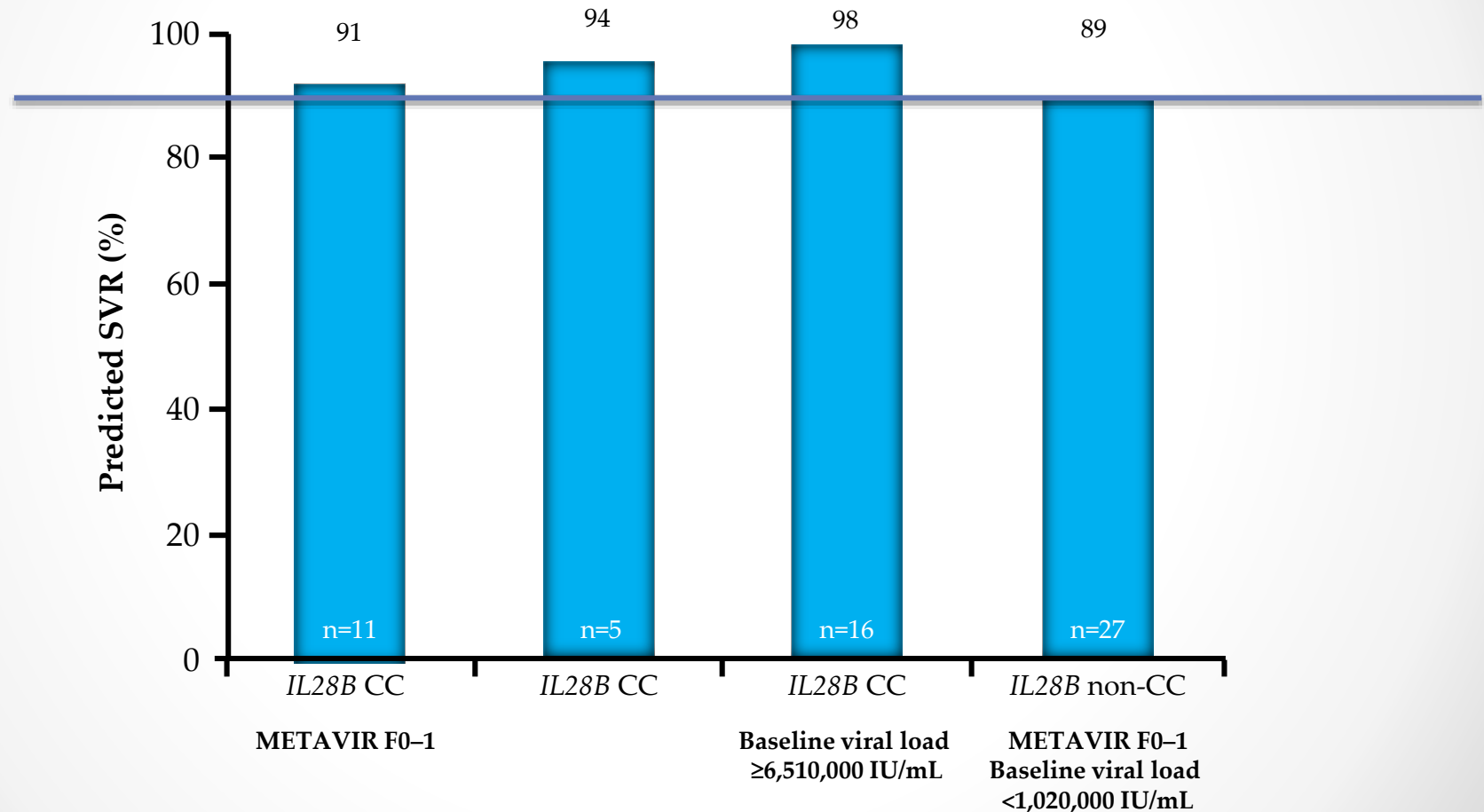
Take home message

- **A cost-effective treatment should respect resource (macro) and individual (micro) allocation criteria**
  - Benefits of HCV therapy/cure extend beyond the liver
  - Disease may reach a point of no return before new therapies become available
- Research focus should gradually shift towards **improving access to care** across diverse and underrepresented populations