Hospital Universitario La Paz

SaludMadrid

Comunidad de Madrid

Del manejo clínico a la inteligencia terapéutica:

cuando **el objetivo es curar**

Dra. M. Montes

Unidad de VIH, Medicina Interna

Hospital Universitario La Paz

Curar la hepatitis C en 2014

- Actualmente en España son candidatos a tratamiento frente a VHC con fármacos antivirales directos (telaprevir/boceprevir):
  - Pacientes infectados por VHC genotipo 1 con fibrosis hepática grado 2,3,4
  - Pacientes coinfectados por VIH/VHC genotipo 1 fibrosis hepática grado 2*, 3, 4.

Curar la hepatitis C en 2014

- Inicialmente la indicación principal de tratamiento con terapias triples frente a VHC han sido:

  – Los pacientes con cirrosis hepática

  – En menor proporción los pacientes con fibrosis avanzada

Curar la hepatitis C en 2014

¿QUÉ PACIENTES CIRRÓTICOS SON HOY CANDIDATOS A TRATAMIENTO CON TELAPREVIR?

¿QUÉ PACIENTES CON FIBROSIS AVANZADA PODEMOS TRATAR HOY DE MANERA EFICAZ Y EVITAR QUE DESARROLLEN CIRROSIS?

EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C 2014

4.12. Treatment of patients with severe liver disease

4.12.1. Compensated cirrhosis

Treatment is strongly recommended for patients with compensated cirrhosis, in order to prevent the complications of chronic HCV infection that occur in this group in the short to mid-term. Indeed, large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decrease of the incidence of clinical decompensation and HCC [63, 64]. However, the SVR rates are generally lower, even with the new therapies, in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis.

EASL Recommendations on Treatment of Hepatitis C 2014, April 2014

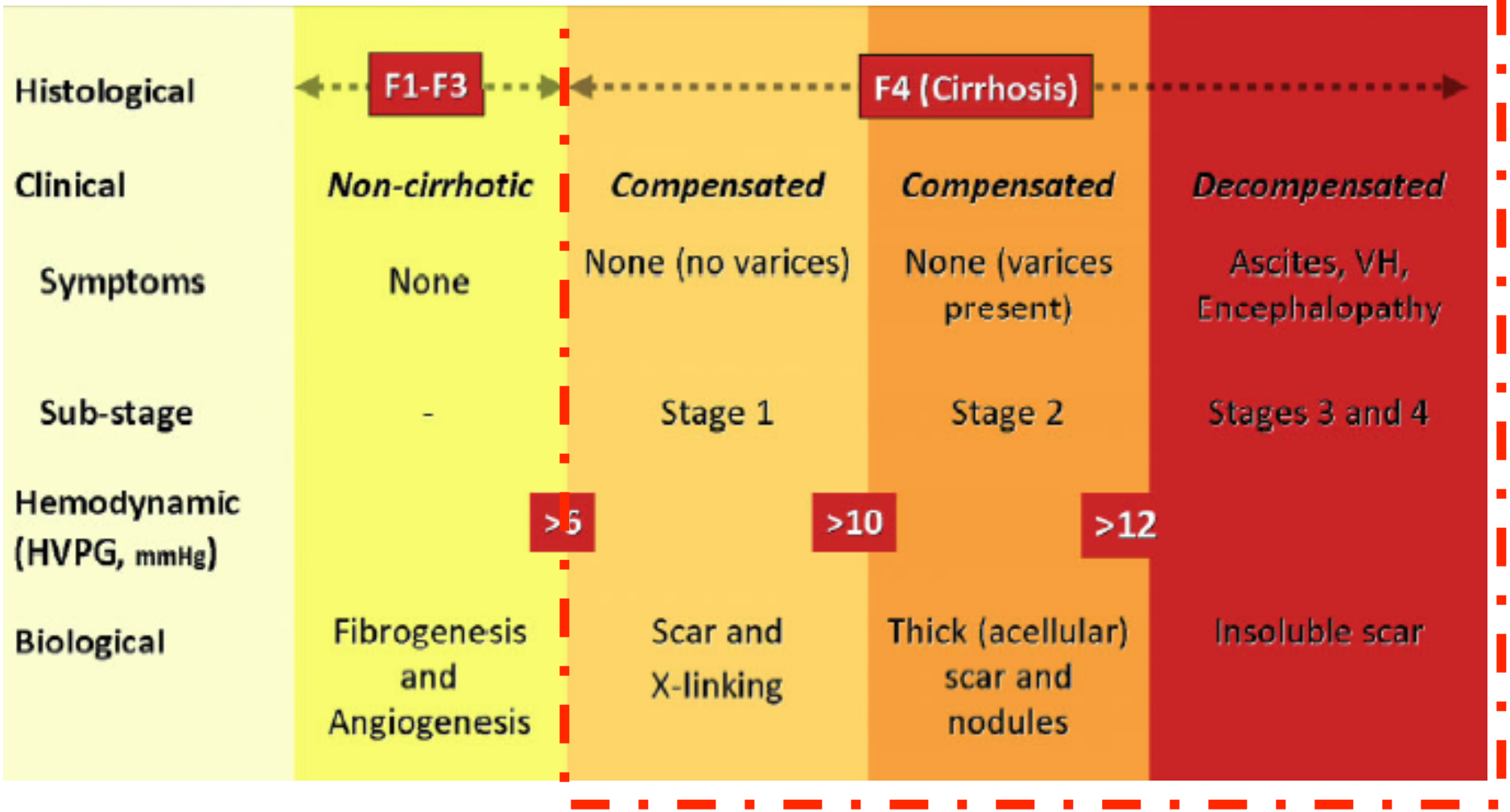
EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C 2014

Recommendations

- Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications **(Recommendation A1)**

EASL Recommendations on Treatment of Hepatitis C 2014, April 2014

PACIENTE CIRRÓTICO: HETEROGENEIDAD CLÍNICA



Garcia-Tsao et al. Hepatology, Vol. 51, No. 4, 2010

PACIENTE CIRRÓTICO: HETEROGENEIDAD CLÍNICA

¿QUÉ NOS PREOCUPA EN ESTOS PACIENTES?

- **Situación clínica:**
  - Riesgo de complicaciones: descompensaciones, hepatocarcinoma, trasplante, muerte…
  - Comorbilidades

- **Oportunidades de Curación:**
  - Grado de Cirrosis y factores predictores de respuesta

- **Efectos adversos del tratamiento**
  - Características basales

PACIENTE CIRRÓTICO: OPCIONES TERAPÉUTICAS

¿Puede este paciente recibir interferón?

- No tratar y esperar a terapias libres de IFN

¿Qué opciones se plantean en estos pacientes?

- Tratamiento con Telaprevir + PegIFN-RBV
- Tratamiento con Boceprevir + PegINF-RBV
- No tratar y esperar a la llegada de nuevos AAD con PegIFN-RBV

CUPIC baseline characteristics: F4 treatment-experienced patients

Baseline characteristic, %	TVR CUPIC[1] N=299	REALIZE F4[2] N=169*	BOC CUPIC[1] N=212	RESPOND 2[3] (BOC44/PR48) F0–F4 N=161
Male	68	75	68	70
Mean/median age, years (range)	57.1 (27–83)	54 (24–68)	56.8 (34–81)	52.3
F4	100	100	100	14
HCV genotype 1 subtype				
1a	34	57	41	60
1b	55	42	49	38
HCV RNA ≥800,000 IU/mL	62	89	64	88
Hb level, g/dL (range)	14.5 (**9.0**–19.7)	15.6 (**12.3**–18.9)	14.8 (**9.1**–18.4)	-
Platelets, /mm^3 (range)	151,000 (**18,000**–604,000)	167,000 (**88,000**–425,000)	144,000 (**33,900**–346,000)	88% >150,000
Serum albumin, g/L (range)	40.0 (**20.7**–53.2)	-	40.4 (**27.0**–50.3)	-
Total bilirubin, µmol/L (range)	15.4 (4.0–**73.5**)	-	15.1 (3.4–**78.0**)	-
Esophageal varices	36	excluded	38	-
Exclusion criteria				
REALIZE	34	-	30	-
RESPOND 2	47		41	

*All arms (TVR arms + control arm)

1. Hézode C, et al. Data presented at the Viral Hepatitis C Congress 2013
2. Pol S, et al. AASLD 2011; Abstract 31
3. Bacon B, et al. N Engl J Med 2011;364:1207–17

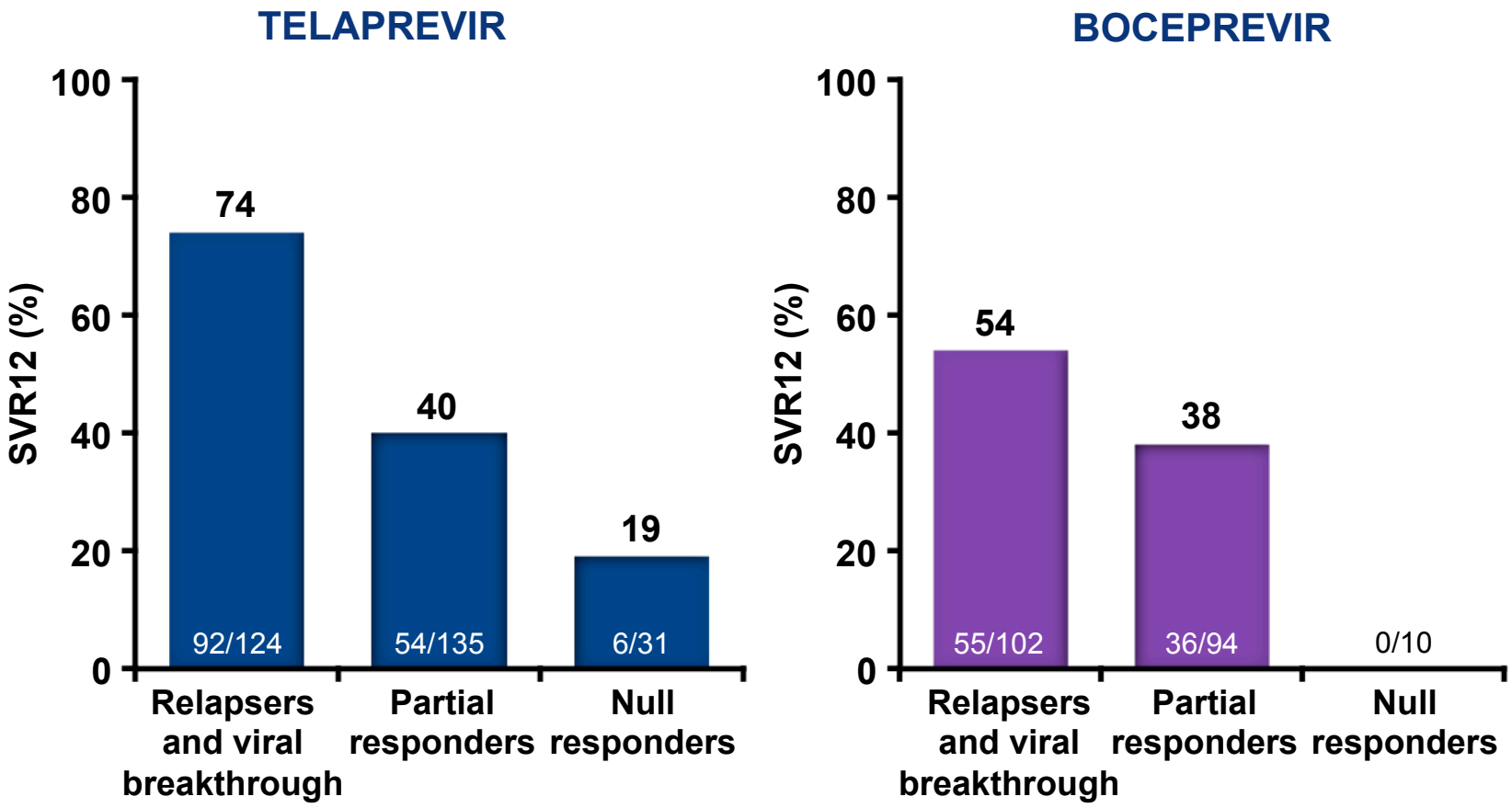
CUPIC: características basales de los pacientes

The primary objective of CUPIC is to **determine the SVR24 rates in HCV patients with cirrhosis**. The interim analysis determined the SVR12 rates

Characteristic	TVR N=299	BOC N=212
Male, %	202 (68)	144 (68)
Mean age, years (range)	57 (27–83)	57 (34–81)
Mean BMI, SD (kg/m^2)	26.5 (4.2)	26.3 (4.3)
HCV genotype 1 subtype, n (%)		
1a	102 (34)	87 (41)
1b	166 (55)	104 (49)
Other	31 (10)	21 (10)
HCV RNA ≥800,000 IU/mL, n (%)	185 (62)	135 (64)
Treatment history, n (%)		
Prior relapse	117 (39)	92 (43)
Prior partial response	135 (45)	94 (44)
Prior null response	31 (10)	10 (5)
Others	16 (6)	16 (8)
Exclusion criteria, n (%)		
REALIZE	101 (34)	63 (30)
RESPOND-2	140 (47)	87 (41)

Fontaine H, et al. Data presented at the AFEF conference 2013

PACIENTE CIRRÓTICO: SVR12 CUPIC (TVR Y BOC)



Hezode C. et al. Gastroenterology 2014 [Epub ahead of print]

TRATAMIENTO DEL PACIENTE CIRRÓTICO CON TELAPREVIR O BOCEPREVIR: CUPIC

Albúmina y plaquetas
Anticipación de los riesgos y complicaciones

CUPIC: RVS12 y el riesgo de aparición de complicaciones graves*

		Recuento plaquetas ≤100,000/mm³	Recuento plaquetas >100,000/mm³
Albúmina <35 g/L	N	37	31
	Complicaciones, n (%)	19 (51.4%)	5 (16.1%)
	SVR12, n (%)	10 (27.0%)	8 (29.0%)
Albúmina ≥35 g/L	N	74	306
	Complicaciones, n (%)	9 (12.2%)	19 (6.2%)
	SVR12, n (%)	27 (36.5%)	168 (54.9%)

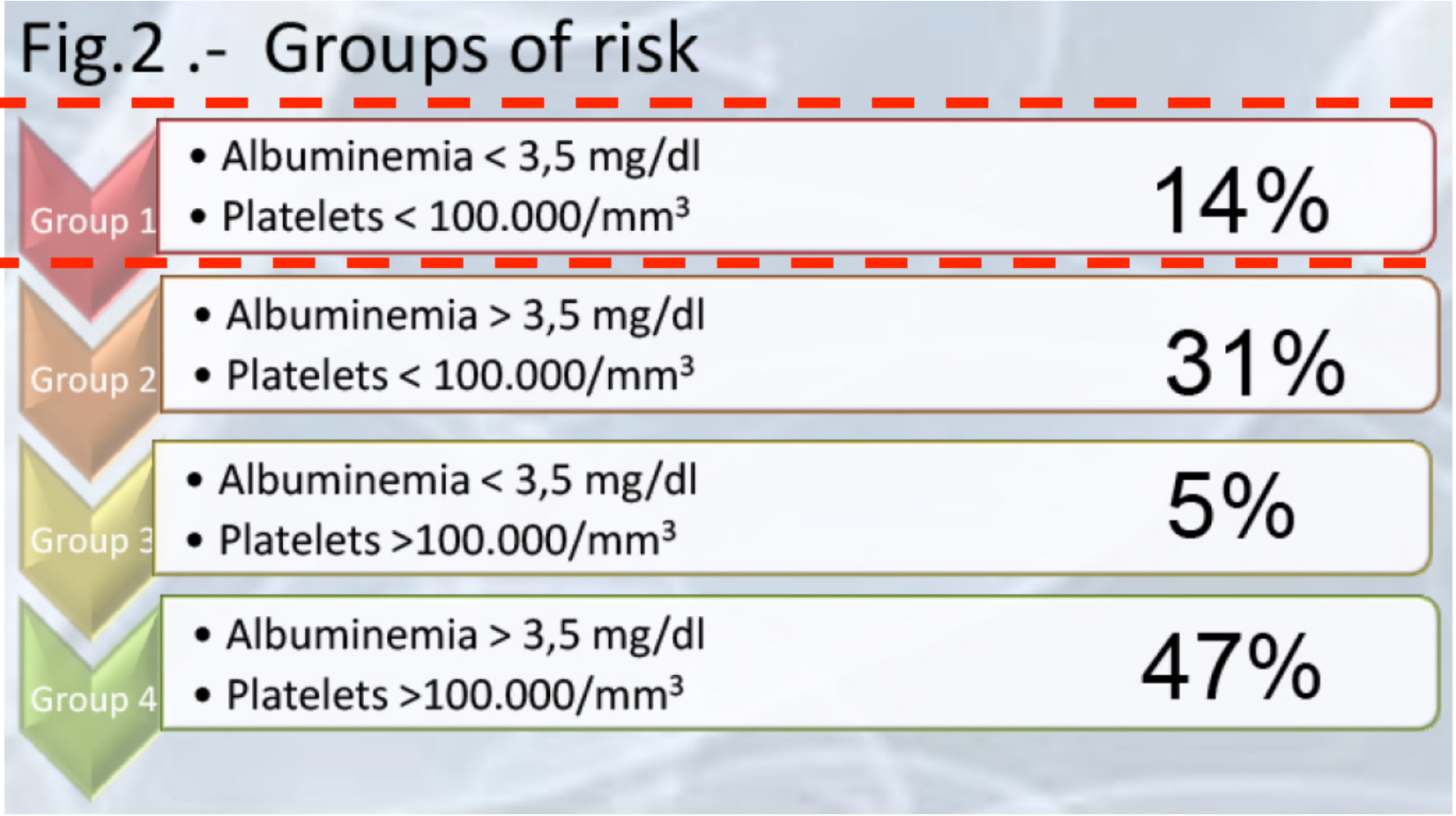
In five recent studies (including a meta-analysis) evaluating the **natural history of cirrhotic patients** with characteristics comparable to those from the CUPIC cohort**, the annual incidence of deaths and/or liver decompensation varied from 6.2 to 11%**,

* Faltan datos de 63 pacientes. Las complicaciones graves incluyen la muerte, hospitalización y descompensación hepática

Hézode C, et al. Data presented at the Viral Hepatitis C Congress 2013

PACIENTES CUPIC

94 PACIENTES CIRRÓTICOS TRATADOS CON TRIPLE TERAPIA EN EL HOSPITAL DE LA FE, VALENCIA



Vinaixa C. et al. EASL 2014

PACIENTE CIRRÓTICO: EVIDENCIAS CON TELAPREVIR

NAIVE

- ADVANCE/ILLUMINATE[1,2] N=1267
- OPTIMIZE[3] N=740
- CONCISE[4] N=239
- PAN cohort[5] N=239
- EAP[6] N=124
- HCV-TARGET[10] N= 320
- Cohorte Prospectiva España[11] N= 177

PRETRATADOS

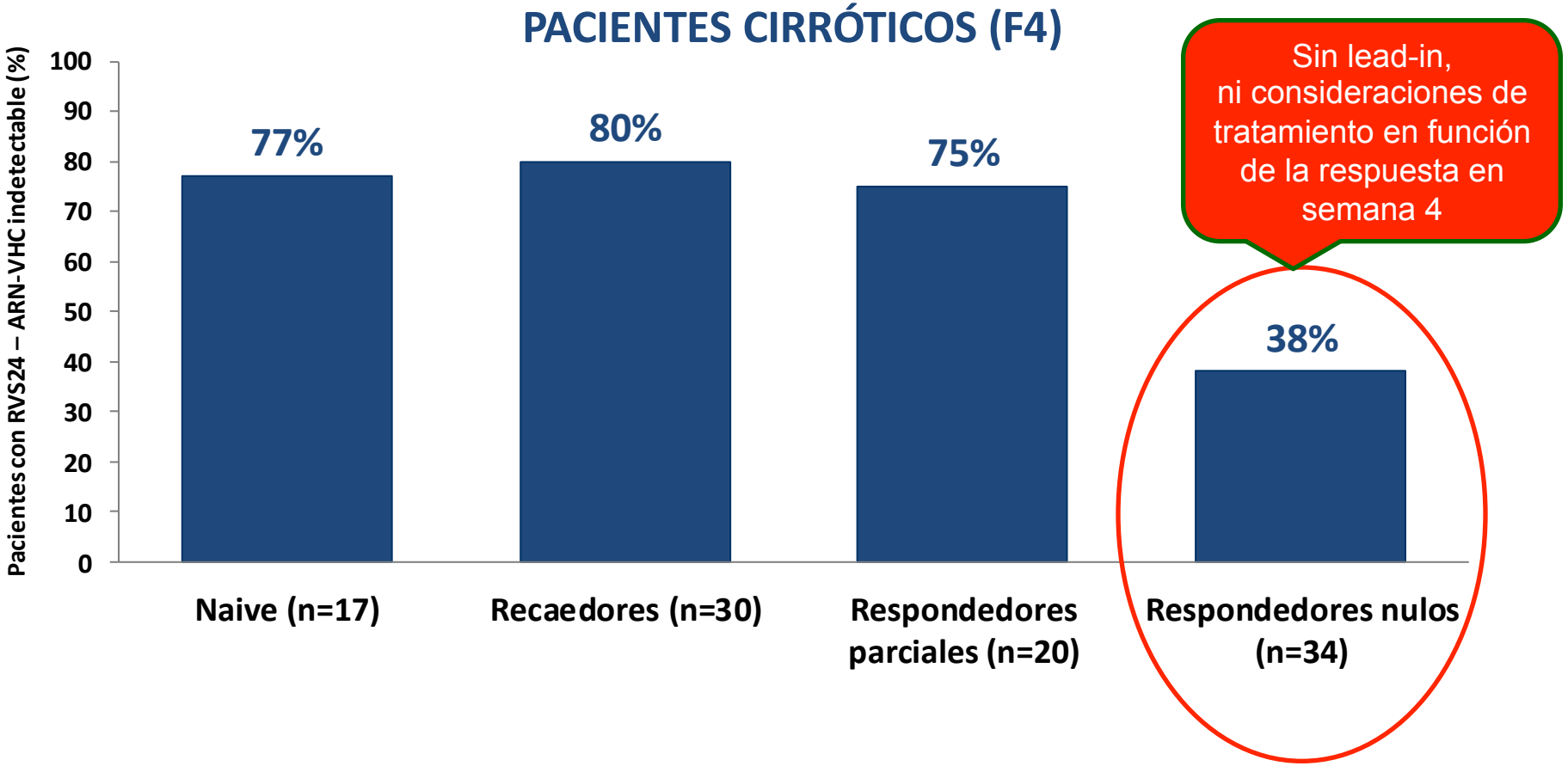
- REALIZE[7] N=530
- C219[13] N=81
- CUPIC[8] N=292
- EAP[6] N=485
- PAN cohort[9] N=537
- HCV-TARGET[10] N= 517
- Cohorte Prospectiva España[11] N= 405

Total >5953 pacientes

Pacientes cirróticos >1848

1. Jacobson I, et al. N Engl J Med 2011;364:2405–16; 2. Sherman KE, et al. N Engl J Med 2011;365:1014–24; 3. Buti M, et al. AASLD 2012; LB-8
4. Nelson DR, et al. EASL 2013: Abstract 881; 5. Mauss S, et al. EASL 2013; Abstract 871; 6. Colombo M, et al. AASLD 2012; Abstract LB-15
7. Zeuzem S, et al. N Engl J Med 2011;364:2417–2; 8. Hézode C, et al. Hepatology 2012;56(Suppl. 1):217A; 9. Christensen S, et al. EASL 2013;Abstract 805.
[10]Di Bisceglie AM, et al. AASLD 2013; Abstract 41; [11]Crespo J, et al. AEEH 2014

PACIENTE CIRRÓTICO: EVIDENCIAS CON TELAPREVIR EN EL EAP ESPAÑOL



Fernández I, et al. Poster #129. AEEH 2014

PACIENTE CIRRÓTICO: Seguridad
EVIDENCIAS CON TELAPREVIR EN EL EAP

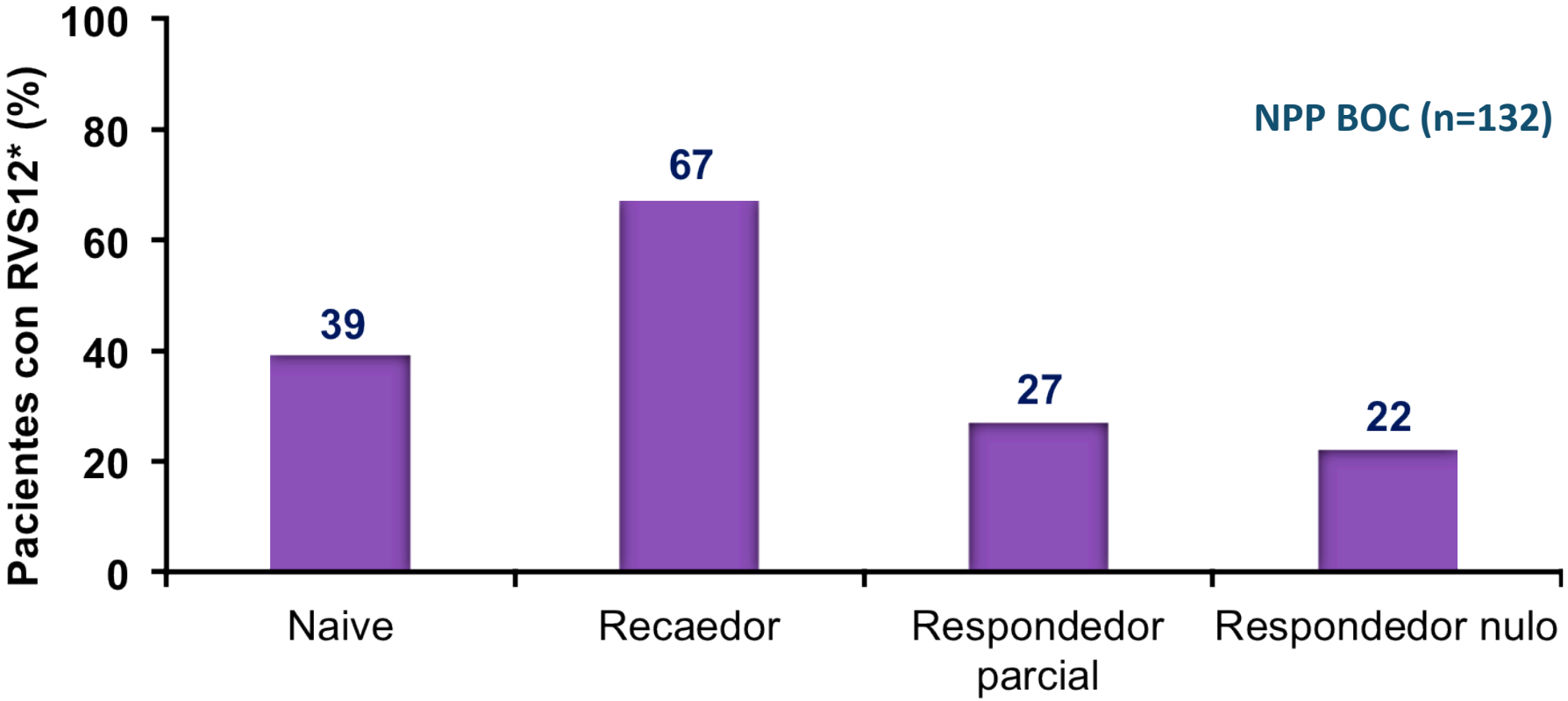
Table 5. Discontinuation of Telaprevir Due to Adverse Events by Fibrosis Status.

Adverse event, n (%)	Bridging fibrosis (F3) (n=746)	Cirrhosis (F4) (n=835)	Overall* (N=1587)
Any event leading to permanent stop of telaprevir	80 (10.7)	113 (13.5)	193 (12.2)

Gaeta GB. et al. Poster #1875. AASLD 2013

PACIENTE CIRRÓTICO: EVIDENCIAS CON BOCEPREVIR EN EL NPP

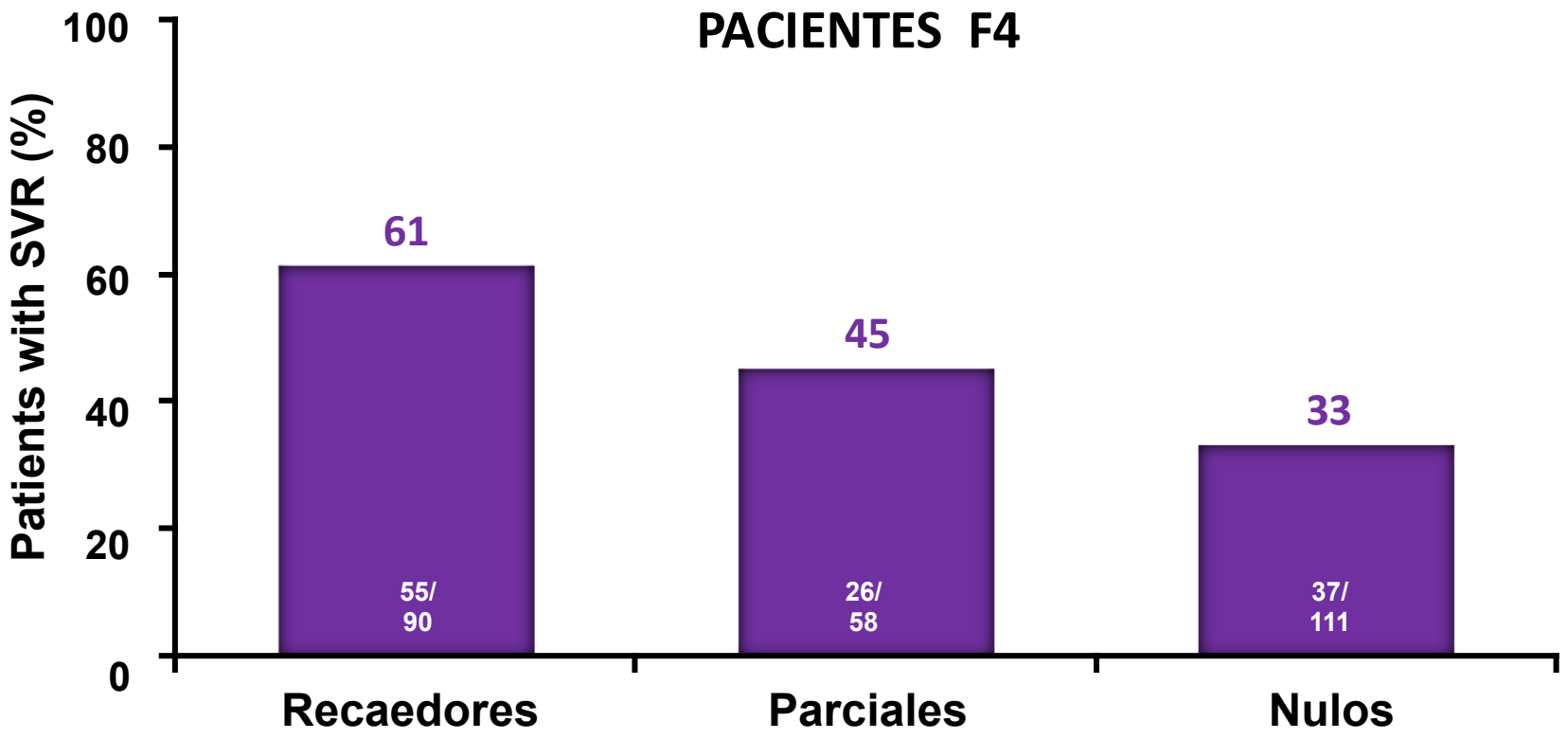
NO DISPONIBLES RESULTADOS POR ESTADIO DE FIBROSIS: INCLUYE PACIENTES CON FIBROSIS AVANZADA Y CIRROSIS



Calleja JL, et al. Poster #1885. AASLD 2013

PACIENTE CIRRÓTICO: EVIDENCIAS CON BOCEPREVIR

EFICACIA DE BOCEPREVIR: RESPUESTA VIRAL SOSTENIDA (RVS12) EN PACIENTES F4 PRETRATADOS



Bruno S. et al. Poster #1158. EASL 2014

PACIENTE CIRRÓTICO:
ADHERENCIA A LA DURACIÓN DE TRATAMIENTO CON BOCEPREVIR

Una adherencia a la duración del tto <80% implica tasas de RVS significativamente menores que adherencias ≥80%

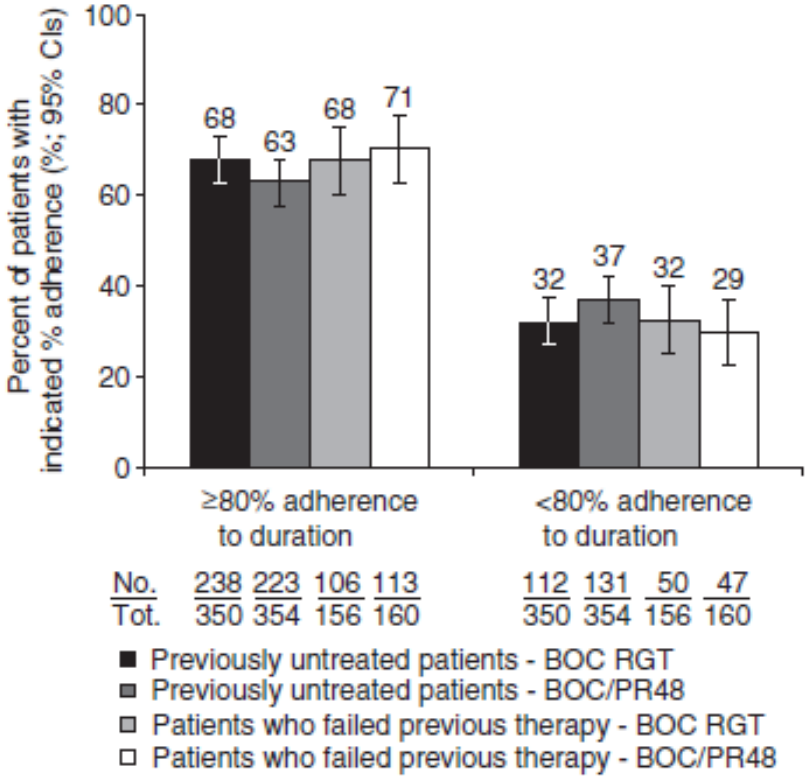


Figure 1 | Per cent of patients who adhered to ≥80% or <80% of their assigned treatment duration.

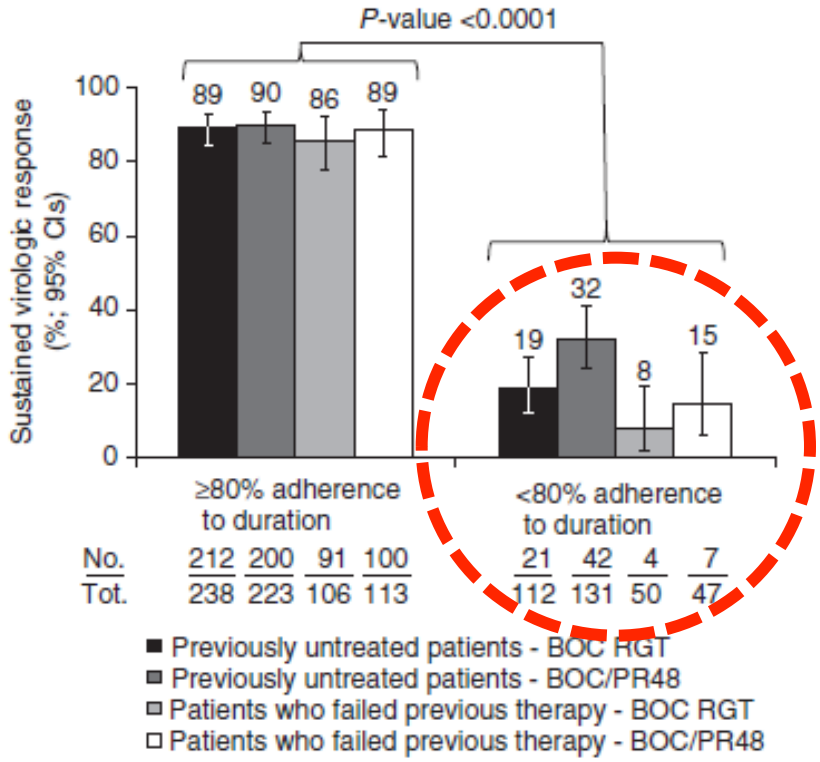


Figure 2 | Sustained virological response (SVR) rates in patients who adhered to ≥80% or <80% of their assigned treatment duration.

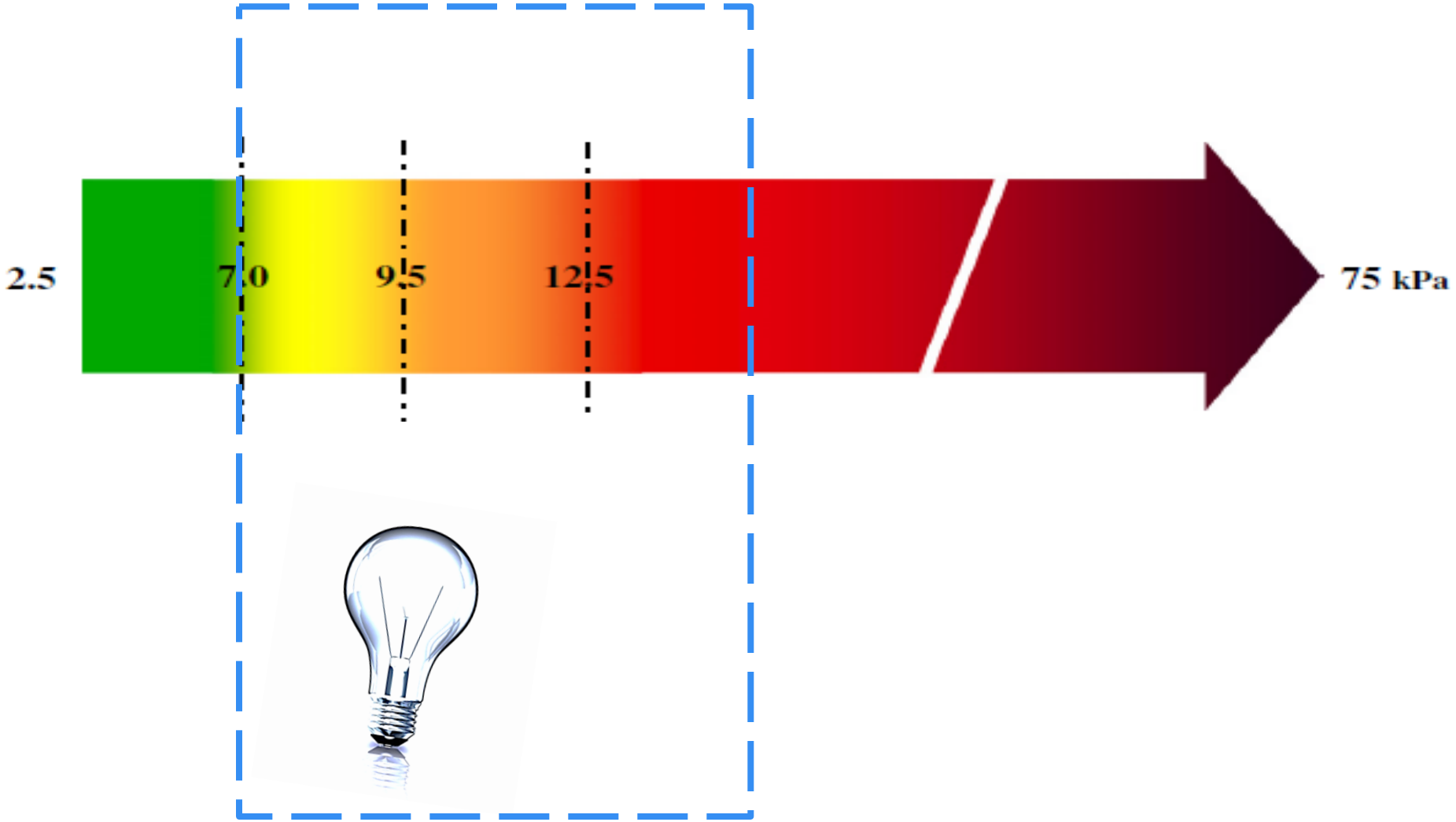
Gordon SC. et al Aliment Pharmacol Ther 2013; 38: 16-27

Curar la hepatitis C en 2014

¿QUÉ PACIENTES CIRRÓTICOS SON HOY CANDIDATOS A TRATAMIENTO CON TELAPREVIR?

¿QUÉ PACIENTES CON FIBROSIS AVANZADA PODEMOS TRATAR HOY DE MANERA EFICAZ Y EVITAR QUE DESARROLLEN CIRROSIS?

EI ESPECTRO DE LA FIBROSIS HEPÁTICA



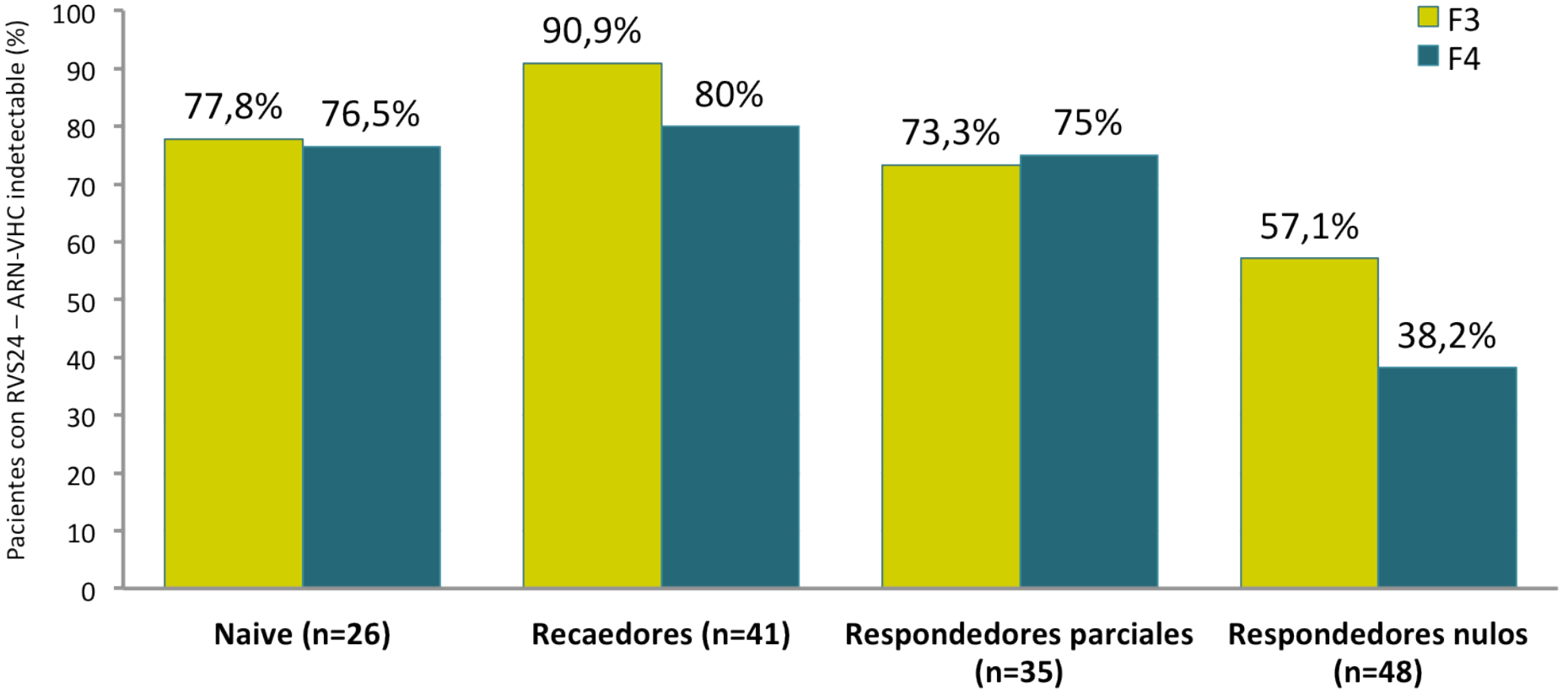
PACIENTE CON FIBROSIS AVANZADA O CIRROSIS (F3-F4): EVIDENCIAS CON TELAPREVIR EN EL EAP ESPAÑOL

Características basales	Fibrosis en puentes (F3) N=50	Cirrosis (F4) N=108	Global N=160
ARN-VHC basal; n(%)			
< 800.000 UI/mL	6 (12%)	25 (23,1%)	32 (20%)
≥ 800.000 UI/mL	44 (88%)	83 (76,9%)	**128 (80%)**
Estadio de fibrosis; n(%)			
Fibrosis en puentes (F3)	50 (100%)	-	**50 (31,3%)**
Cirrosis (F4)	-	108 (100%)	**108 (67,5%)**
Genotipo del VHC			
1a	13 (26%)	27 (25%)	40 (25%)
1b	34 (68%)	79 (73,1%)	113 (70,6%)
No realizado o desconocido	3 (6%)	2 (1,9%)	7 (4,4%)
Genotipo IL28B			
Desconocido	21 (42%)	60 (55,6%)	**82 (51,3%)**
CC	5 (10%)	10 (9,3%)	15 (9,4%)
CT	18 (36%)	26 (24, 1%)	**45 (28,1%)**
TT	6 (12%)	12 (11,1%)	**18 (11,3%)**

Fernández I, et al. Poster #129. AEEH 2014

PACIENTE CON FIBROSIS AVANZADA: EVIDENCIAS CON TELAPREVIR EN EL EAP ESPAÑOL

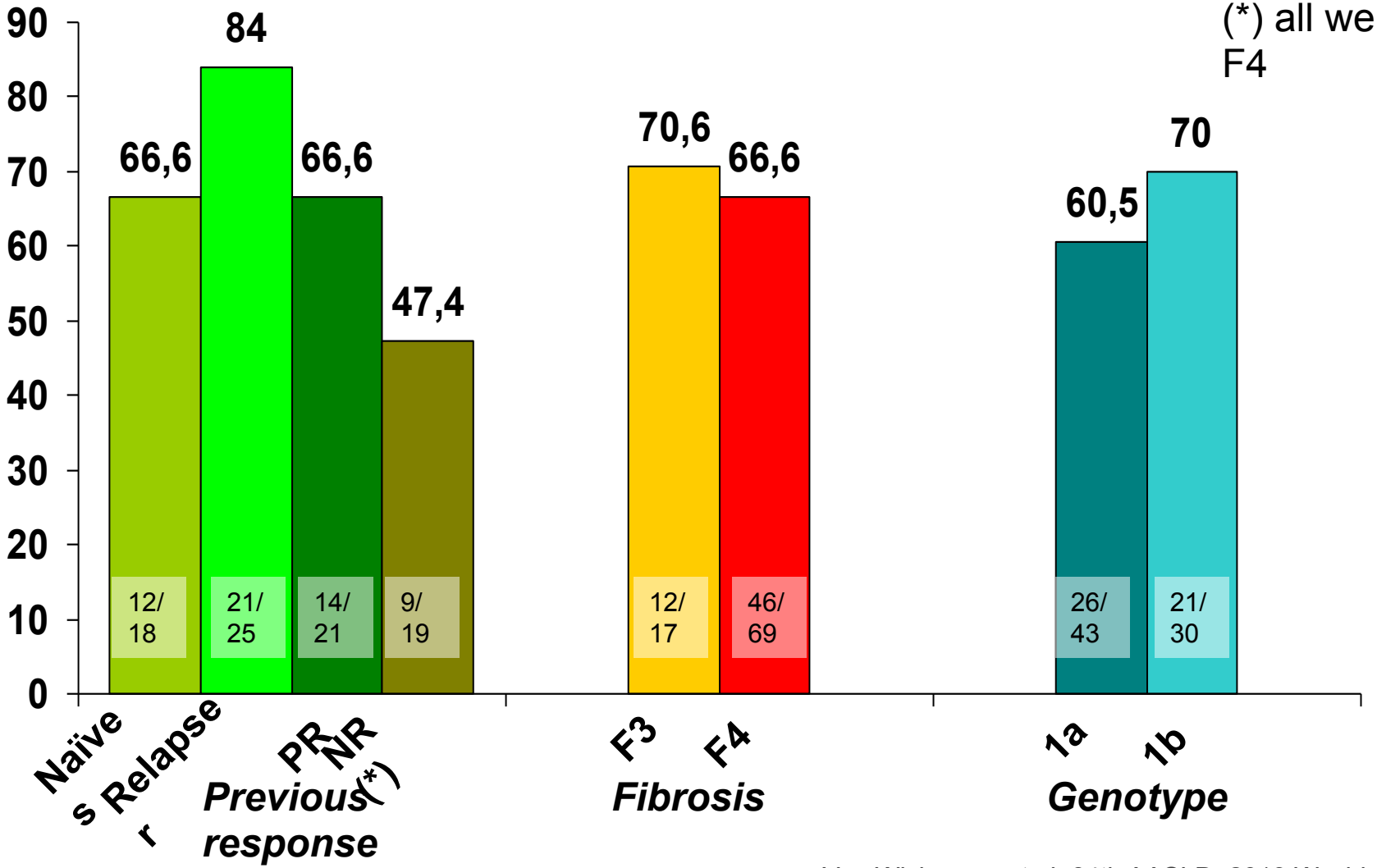
Curación (RVS24) con Telaprevir por estadio de fibrosis y respuesta previa



* Fibrosis no bien definida en un paciente recaedor y un respondedor parcial previos

Fernández I, et al. Poster #129. AEEH 2014

Cohorte española VIH-VHC: Eficacia % indetectabilidad RNA VHC (ITT)



Von Wichmann et al, 64th AASLD, 2013 Washington

PACIENTE CON FIBROSIS AVANZADA: SEGURIDAD EVIDENCIAS CON TELAPREVIR EN EL EAP ESPAÑOL

Efectos adversos grado 2-4 relacionados con el tto. antiviral por estadio de fibrosis (≥ 5% de pacientes)

Efecto Adverso	F3 N=50	F4 N=108	Global N=160
Pacientes con 1 o más efectos adversos al menos grado 2	42 (84,0%)	84 (77,8%)	126 (78,8%)
Anemia SSC	29 (58,0%)	62 (57,4%)	91 (56,9%)
Trombopenia SSC	10 (20,0%)	23 (21,3%)	33 (20,6%)
Astenia	9 (18,0%)	18 (16,7%)	27 (16,9%)
Exantema SSC	6 (12,0%)	17 (15,7%)	23 (14,4%)
Hiperuricemia	6 (12,0%)	15 (13,9%)	21 (13,1%)
Prurito SSC	4 (8,0%)	13 (12,0%)	17 (10,6%)
Síntomas ano-rectales SSC	3 (6,0%)	11 (10,2%)	14 (8,8%)

Fernández I, et al. Poster #129. AEEH 2014

PACIENTE CIRRÓTICO: OPCIONES TERAPÉUTICAS

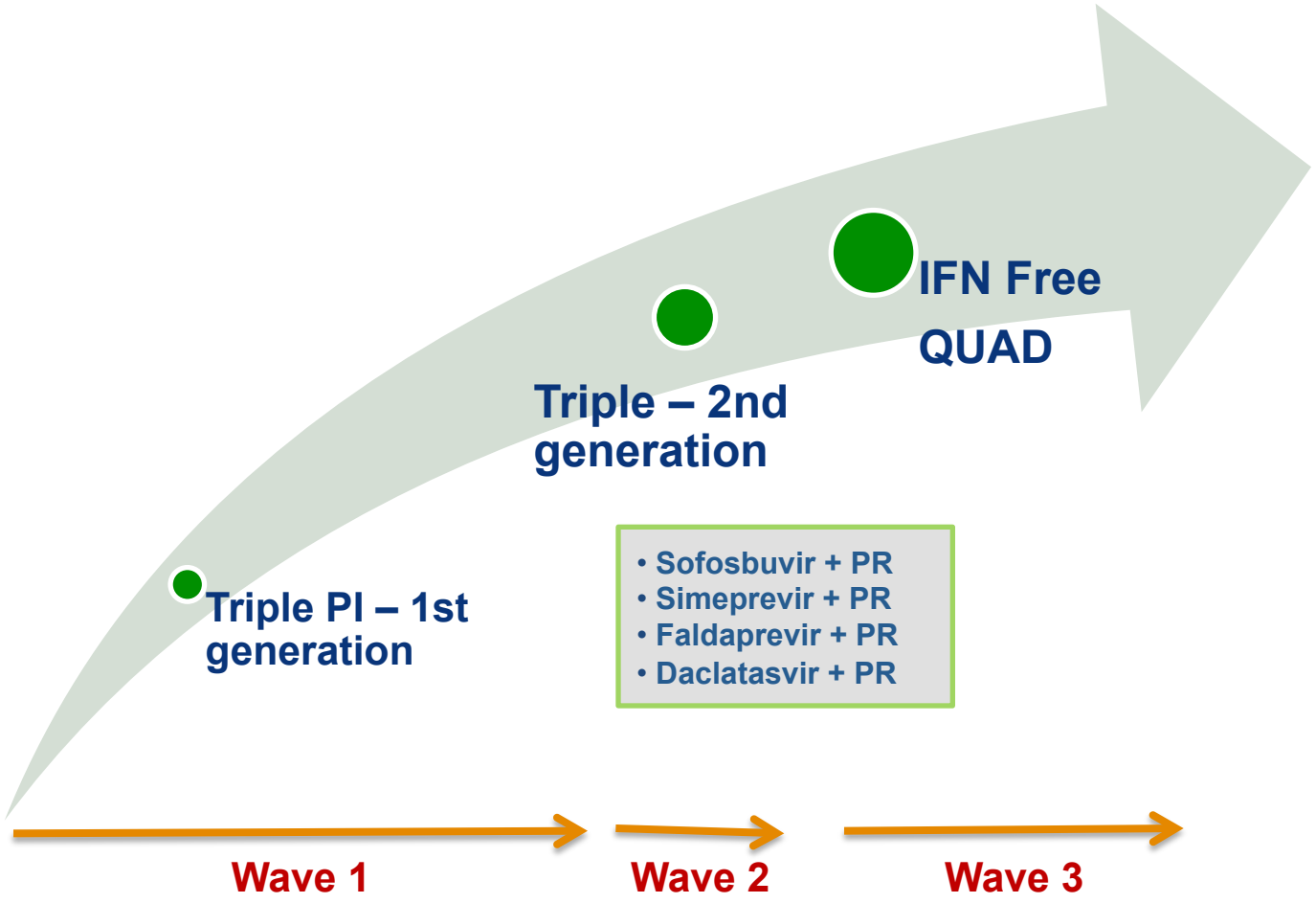
¿Puede este paciente recibir interferón?

- **No tratar y esperar a terapias libres de IFN**

¿Qué opciones se plantean en estos pacientes?

- Tratamiento con Telaprevir + PegIFN-RBV
- Tratamiento con Boceprevir + PegINF-RBV
- **No tratar y esperar a la llegada de nuevos AAD con PegIFN-RBV**

DISPONIBILIDAD DE NUEVOS FÁRMACOS…



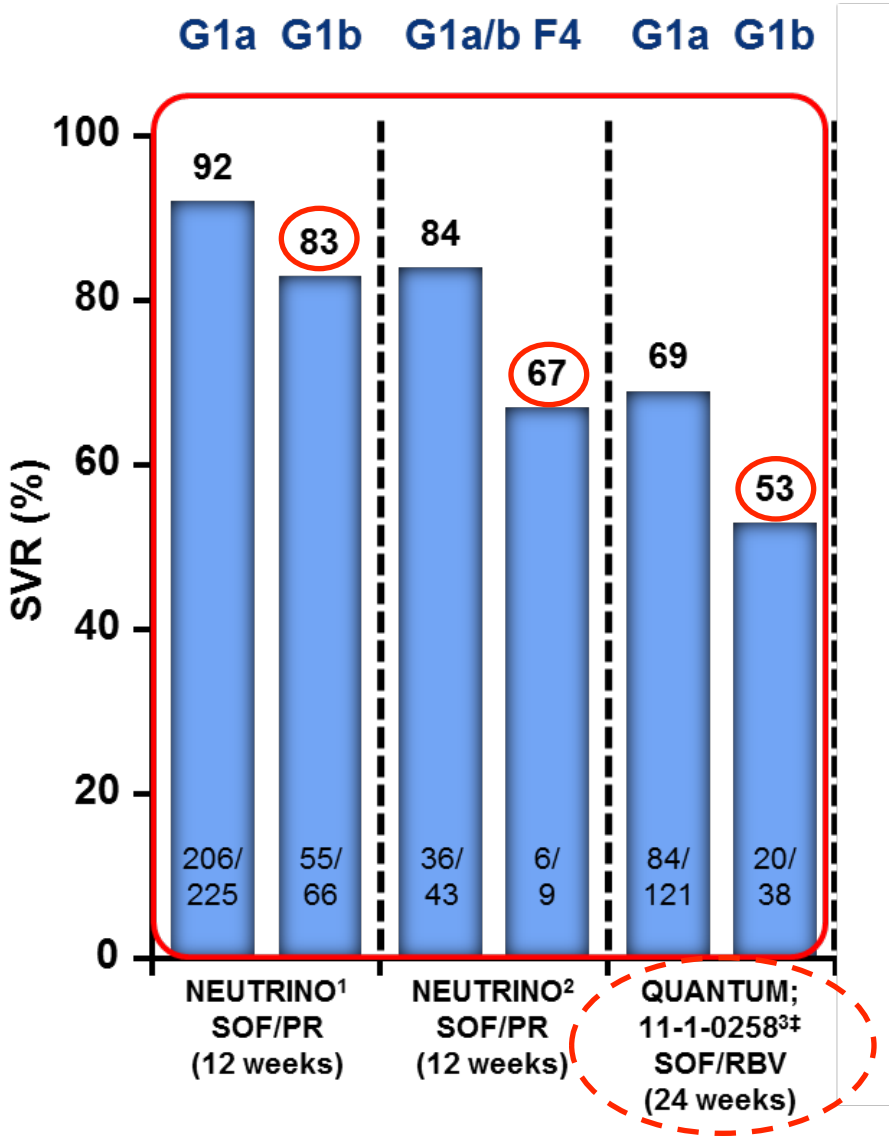
PACIENTE CIRRÓTICO:
EVIDENCIAS CON SOFOSBUVIR + PegIFN-RIBAVIRINA

Ensayos de Fase III con Sofosbuvir

NOMBRE	GENOTIPOS	n PACIENTES	RVS
FISSION	2	70	97
	3	183	56
POSITRON	2	109	93
	3	98	61
FUSSION (12 sem)	2	36	86
	3	64	30
FUSSION (16 sem)	2	32	94
	3	63	62
NEUTRINO	1	292	89
	4	28	96
	5/6	7	100

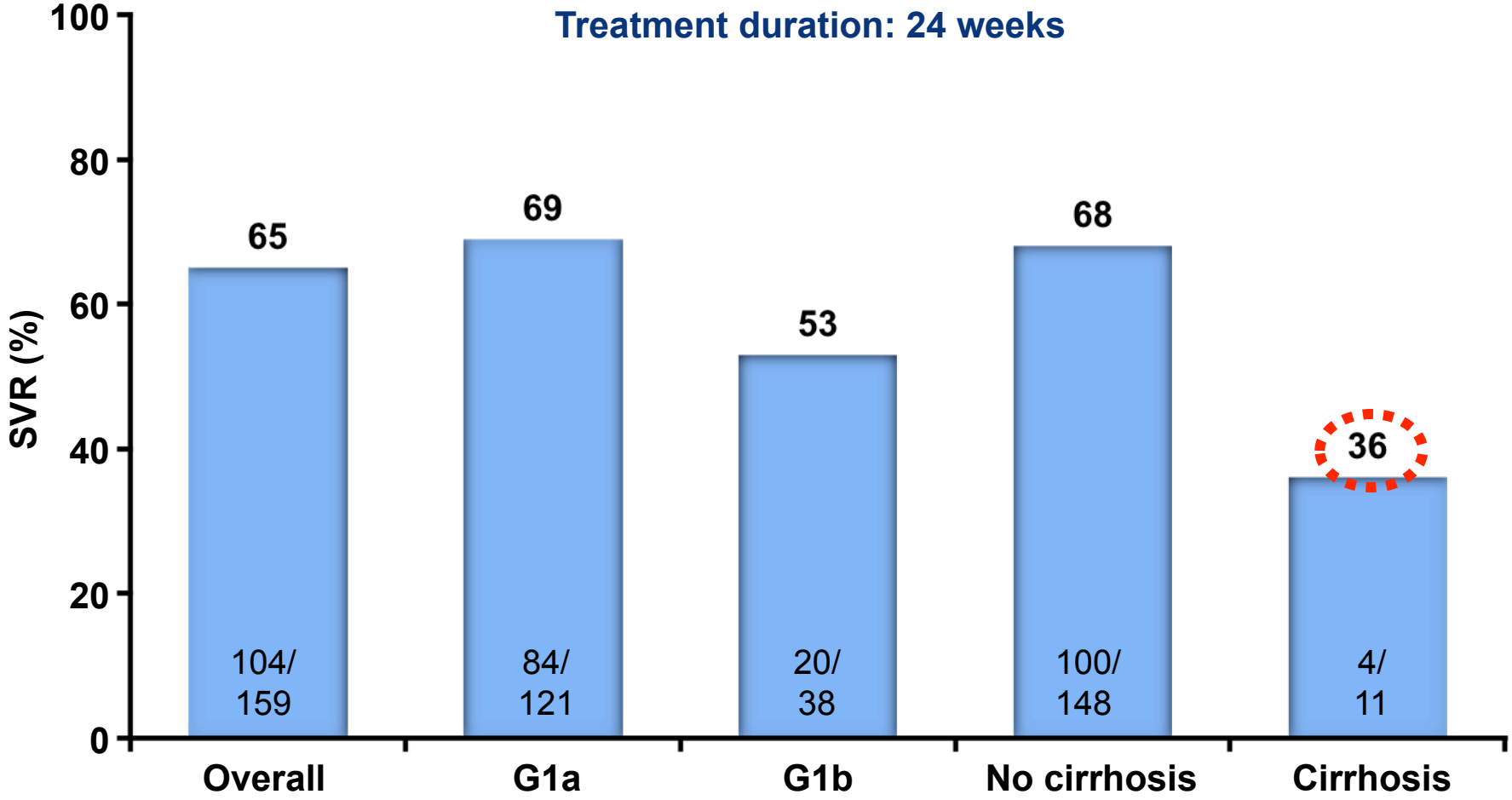
18% F4

PACIENTE CIRRÓTICO:
EVIDENCIAS CON SOFOSBUVIR + PegIFN-RIBAVIRINA



PACIENTE CIRRÓTICO:
EVIDENCIAS CON SOFOSBUVIR + RIBAVIRINA (SIN INTERFERÓN)

Sofosbuvir + RBV efficacy in G1 HCV (Phase 2 studies*)



*data from QUANTUM and 11-1-0258 studies
These are exploratory or Phase 2 studies; the outcome should be interpreted with caution since patient numbers are small and SVR rates may be impacted by the selection of patients

Sofosbuvir EU SmPC

Table 3. Adverse Events, Discontinuation of Treatment, and Hematologic Abnormalities.*

Event	NEUTRINO Study	FISSION Study	
	SOF+PEG+RBV for 12 Weeks (N=327)	SOF+RBV for 12 Wk (N=256)	PEG+RBV for 24 Wk (N=243)
Mean duration of treatment — wk	12±1	12±2	21±6
Discontinuation because of an adverse event — no. (%)	5 (2)	3 (1)	26 (11)
Any serious adverse event during treatment — no. (%)	4 (1)	7 (3)	3 (1)
Any adverse event during treatment — no. (%)	310 (95)	220 (86)	233 (96)
Common adverse events — no. (%)†			
Fatigue	192 (59)	92 (36)	134 (55)
Headache	118 (36)	64 (25)	108 (44)
Nausea	112 (34)	46 (18)	70 (29)
Insomnia	81 (25)	31 (12)	70 (29)
Anemia	68 (21)	20 (8)	28 (12)
Decreased appetite	58 (18)	17 (7)	44 (18)
Influenza-like illness	51 (16)	7 (3)	44 (18)
Chills	54 (17)	7 (3)	43 (18)
Pyrexia	58 (18)	6 (2)	33 (14)
Rash	59 (18)	23 (9)	43 (18)
Diarrhea	38 (12)	23 (9)	42 (17)
Pruritus	54 (17)	19 (7)	42 (17)
Myalgia	45 (14)	21 (8)	40 (16)
Irritability	42 (13)	25 (10)	40 (16)
Neutropenia	54 (17)	0	30 (12)

Table 3. Adverse Events, Discontinuation of Treatment, and Hematologic Abnormalities.*

Event	NEUTRINO Study	FISSION Study	
	SOF+PEG+RBV for 12 Weeks (N=327)	SOF+RBV for 12 Wk (N=256)	PEG+RBV for 24 Wk (N=243)
Hematologic event — no. (%)‡			
Decreased hemoglobin level			
<10 g/dl	74 (23)	23 (9)	35 (14)
<8.5 g/dl	8 (2)	1 (<1)	4 (2)
Decreased lymphocyte count			
350 to 500/mm³	17 (5)	0	15 (6)
<350/mm³	0	0	12 (5)
Decreased neutrophil count			
500 to 750/mm³	49 (15)	0	30 (12)
<500/mm³	17 (5)	0	6 (2)
Platelet count <50,000/mm³	1 (<1)	0	18 (7)
Decreased white-cell count			
1000 to 1500/mm³	18 (6)	0	10 (4)
<1000/mm³	0	0	1 (<1)


SEGURIDAD
EFICACIA

PREDICTION OF SUSTAINED VIROLOGIC RESPONSE IN TREATMENT-NAIVE CHRONIC HEPATITIS C GENOTYPE 1 PATIENTS TREATED WITH TELAPREVIR PLUS PEGYLATED INTEFERON AND RIBAVIRIN IN PHASE 3 TRIALS

S. Zeuzem1, R. Demasi2, G.R. Foster3, M. Buti4, A. Baldini5, D. Luo2, J. Witek2, M. Rizzetto6

1Department of Internal Medicine, J. W. Goethe University Hospital I, Frankfurt, Germany, 2Janssen Research & Development LLC, Titusville, NJ, United States, 3Queen Mary Hospital, University of London, Barts Health, London, United Kingdom, 4Hospital Valle Hebron, Barcelona, Spain, 5Janssen-Cilag, Paris, France, 6Univeristy of Torino, Torino, Italy

E-mail: zeuzem@em.uni-frankfurt.de

Poster 1120

STUDY DESIGN

- Safety and efficacy **data for 1643 treatment-naïve patients who were treated with TVR for 12 weeks plus PR in three Phase III, randomised, clinical studies were pooled: ADVANCE (n=363), ILLUMINATE (n=540) and OPTIMIZE (n=740)**

- **<u>Statistical analyses</u>: baseline and on-treatment predictive factors of SVR were analysed using a multivariate linear regression analysis with SVR as the dependent variable.**

- Zeuzem S, et al. EASL 2014

EFFICACY/RESULTS

- **Baseline predictors of SVR**: the multivariate analysis identified five significant baseline predictors of SVR:
  - AFP<10ug/L
  - Baseline HCV RNA<800000 iU/mL
  - Platelets>150000/uL
  - Fibrosis stage F0-2 (vs F3-4)
  - HCV Genotipe 1b (vs 1a)

- **The five baseline factors remained predictive of SVR after inclusion of RVR in the model**

- Zeuzem S, et al. EASL 2014

EFFICACY/RESULTS

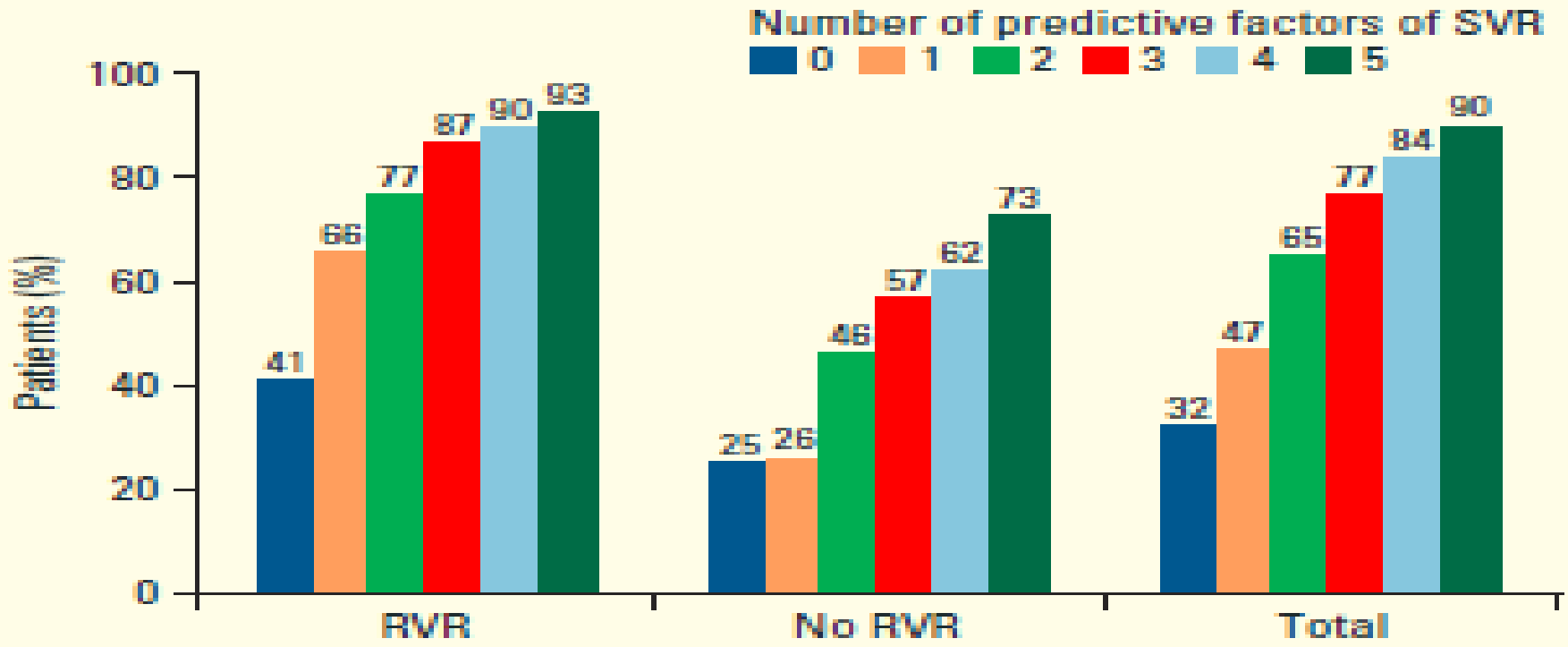


Figure 4. Proportion of Patients Achieving SVR According to the Number of Baseline Predictive Factors of SVR.

SAFETY

- **Grade 2-4 adverse events** were reported by 75%, 79%, 85% and **88%** of patients with F0-F1, F2, F3 and **F4 fibrosis** respectively.

- **Serious adverse events** were reported by 9%, 10&, 11% and 17% of patients with F0-F1, F2, F3 and F4 fibrosis, respectively

- **Discontinuations** due to adverse events were **significantly more likely in patients with F3 or F4 stage fibrosis (13-15%)** in comparison with patients with F0-F2 fibrosis (8-12%) (P=0,028)

PREDICTORS OF SVR24 FOR 1078 PATIENTS WITH SEVERE FIBROSIS OR COMPENDATED CIRRHOSIS: THE INTERNATIONAL TELAPREVIR ACCESS PROGRAM

M. Colombo, S.I. Strasser, C. Moreno, P.A. Ferreira, P. Urbanek,

I. Fernández, D. Abdurakhmanov, A. Streinu-Cercel, A. Verheyen, W. Iraqi, R. Demasi, A. Hill, I. Lonjon-Domanec, H. Wedemeyer.

Poster 1210

EFFICACY/RESULTS

- SVR rate by number of positive predictive factors (PPFs):

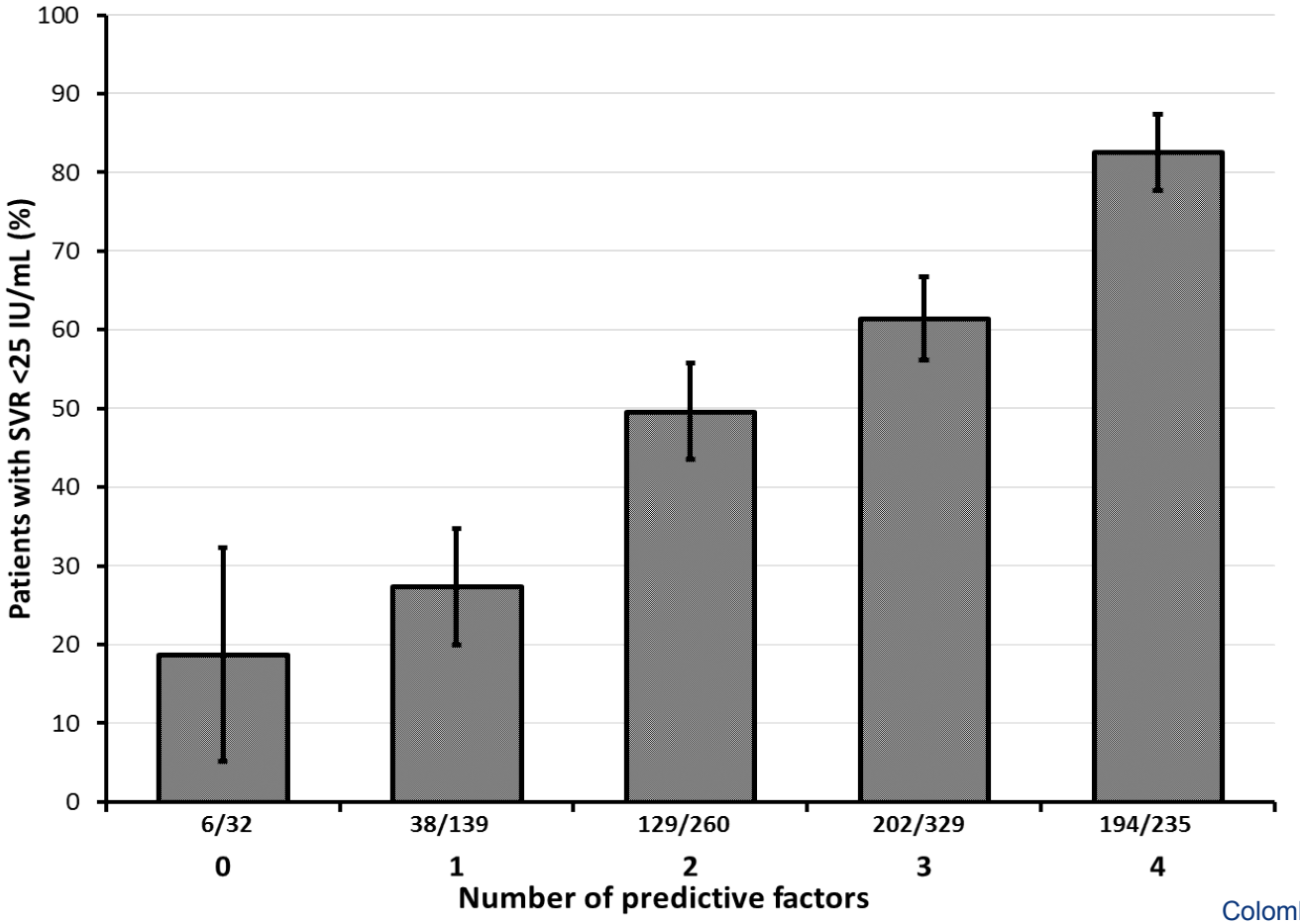
The proportion of patients achieving SVR24 <25 IU/mL by the number of predictive factors that were identified in the multivariate analysis:

- **AFP<10µg/L,**
- **Fibrosis (F3 vs. F4),**
- **Genotype (1b vs. 1a/other),**
- **Prior response (other vs. null response).**

Colombo et al. EASL 2014

EFFICACY/RESULTS

The SVR rate rose from 19% for patients with no positive predictive factors to 83% for patients with 4 positive predictive factors



Colombo et al. EASL 2014

Inteligencia terapéutica y OPTIMIZACIÓN: FACTORES PREDICTORES DE RVS CON TELAPREVIR

PREDICTORS NAIVE

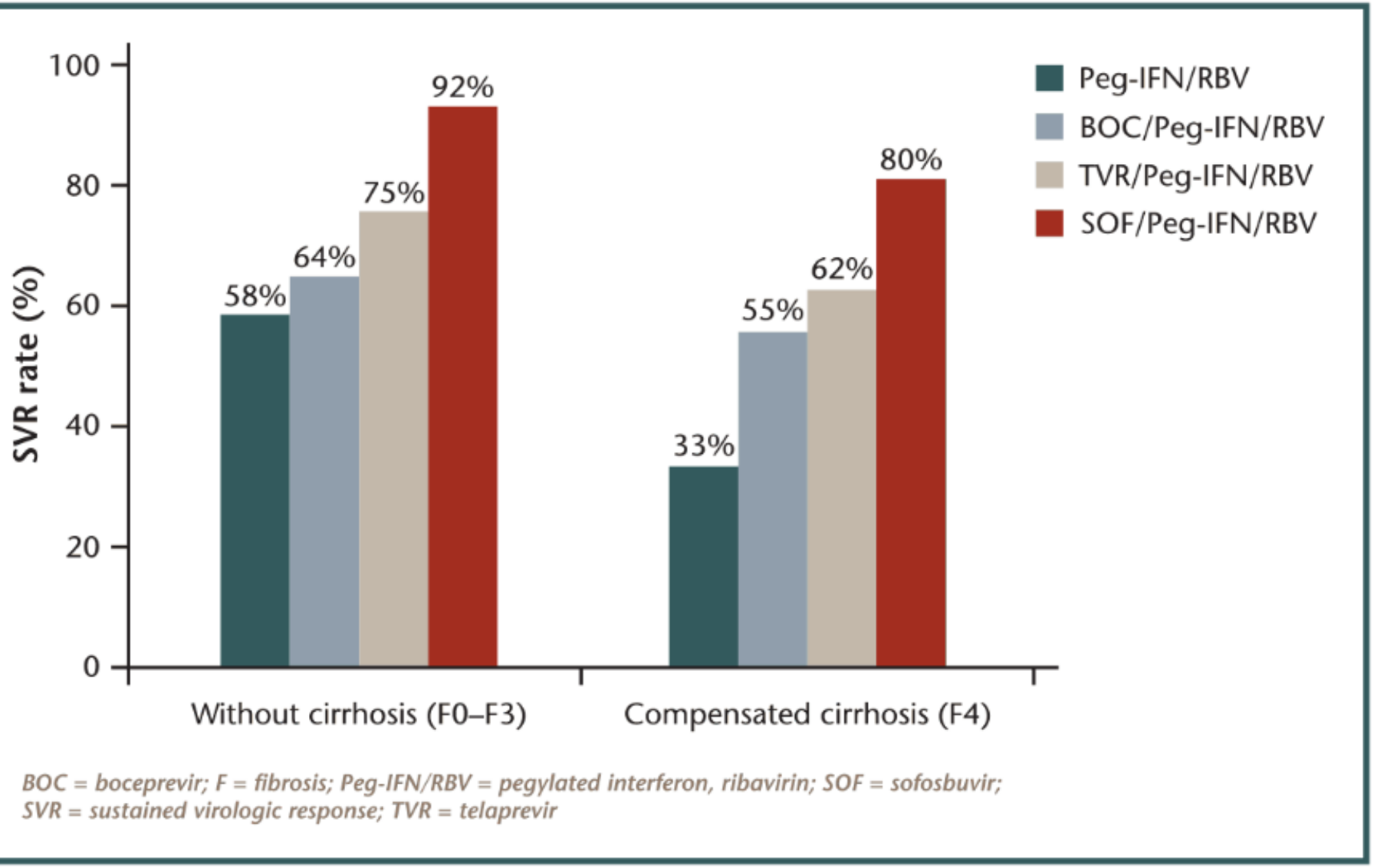
1. AFP <10 µg/L
2. Baseline HCV RNA <800,000 IU/mL
3. Platelets ≥150,000/µL
4. F0–F2 fibrosis stage (vs F3–F4)
5. HCV G1b (vs 1a)

PREDICTORS F3-F4

1. AFP <10 µg/L
2. Baseline HCV RNA <800,000 IU/mL
3. Platelets ≥150,000/µL
2. Fibrosis (F3 vs F4)
3. HCV G1b (vs 1a)
4. Prior response (other vs. null)

Zeuzem S, et al. EASL 2014; Colombo et al. EASL 2014

Figure 2. Treatment efficacy: sustained virologic response rates by treatment regimen and cirrhosis status



BOC = boceprevir; F = fibrosis; Peg-IFN/RBV = pegylated interferon, ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; TVR = telaprevir

¿QUÉ PACIENTES CIRRÓTICOS NO SON HOY CANDIDATOS A TRATAMIENTO CON TELAPREVIR?

- Pacientes con contraindicación a interferón y/o ribavirina
- Cirrosis descompensada
- Pacientes null-responder sin ningún otro factor predictor de respuesta
- Pacientes con plaquetas y albúmina baja

¿QUÉ PACIENTES CON FIBROSIS AVANZADA NO SON HOY CANDIDATOS A TRATAMIENTO CON TELAPREVIR?

- Pacientes con contraindicación a interferón y/o ribavirina
- Pacientes null-responder sin ningún otro factor predictor de respuesta
- Pacientes con plaquetas y albúmina baja