Hospital Universitario
Puerta de Hierro Majadahonda

SaludMadrid

Comunidad de Madrid

VHC: Nuevo documento de la AEMPS

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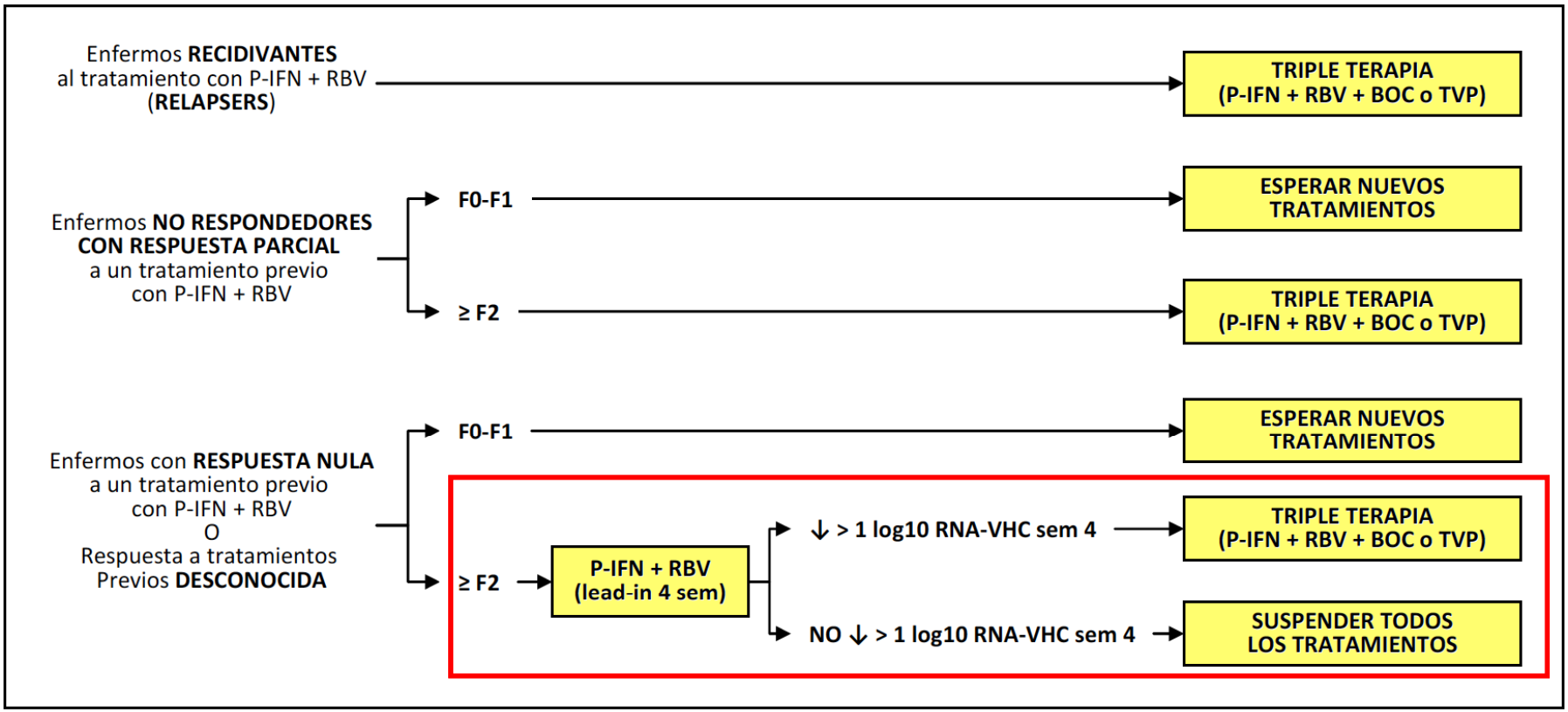
INVESTIGACIÓN
PUERTA DE HIERRO

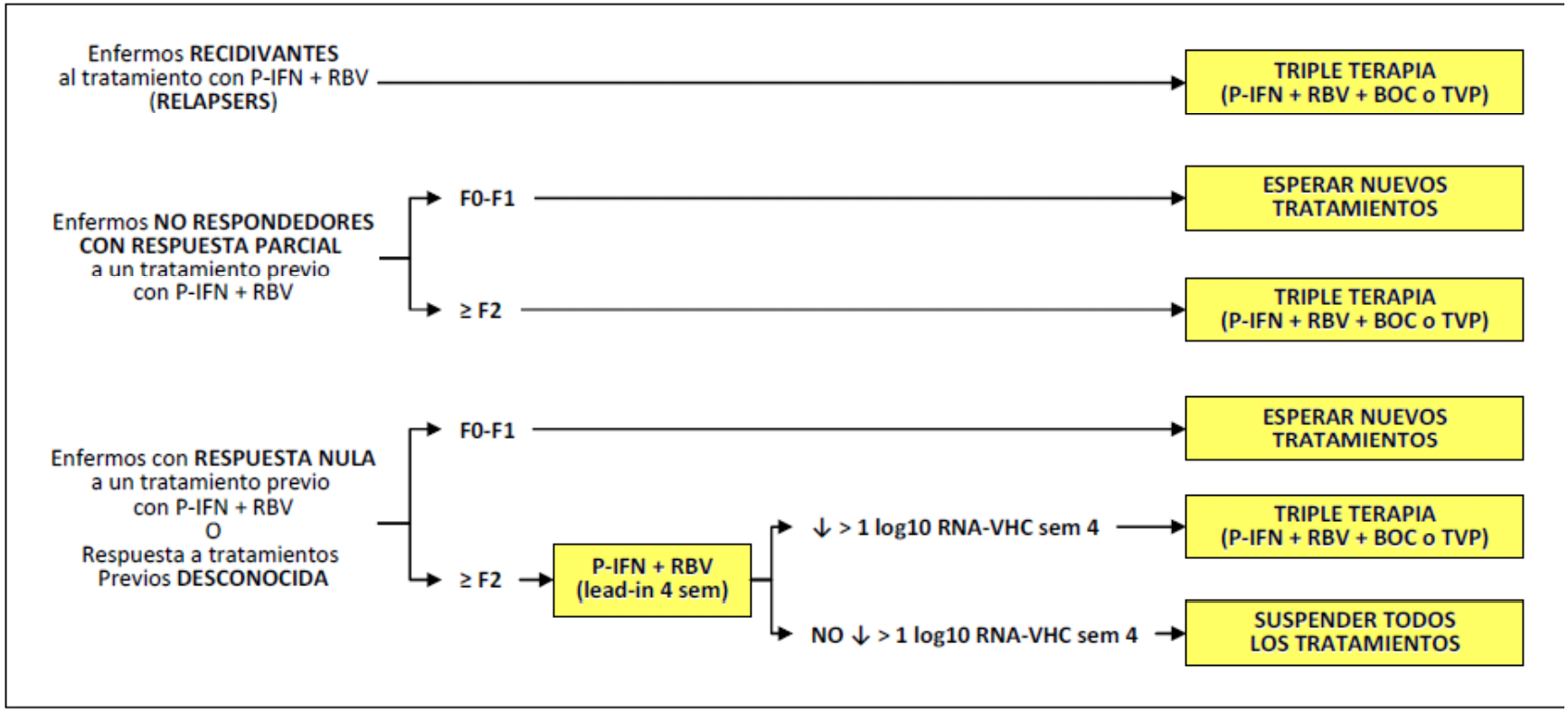
Recomendaciones para el tratamiento de los pacientes G1 no respondedores en España



GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD
SECRETARÍA GENERAL DE SANIDAD Y CONSUMO
DIRECCIÓN GENERAL DE CARTERA BÁSICA DE SERVICIOS DEL SISTEMA NACIONAL DE SALUD Y FARMACIA
agencia española de medicamentos y productos sanitarios

http://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/criterios-VHC-monoinfectados_28-02-12.pdf

Pacientes tratados con PEG+RIBA



Documentos de la AEMPS

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agencia española de medicamentos productos sanitarios

TRATAMIENTO DE LA HEPATITIS CRÓNICA C (VHC)

1. **CRITERIOS Y RECOMENDACIONES GENERALES PARA EL TRATAMIENTO CON BOCEPREVIR Y TELAPREVIR DE LA HEPATITIS CRÓNICA C (VHC) EN PACIENTES MONOINFECTADOS**

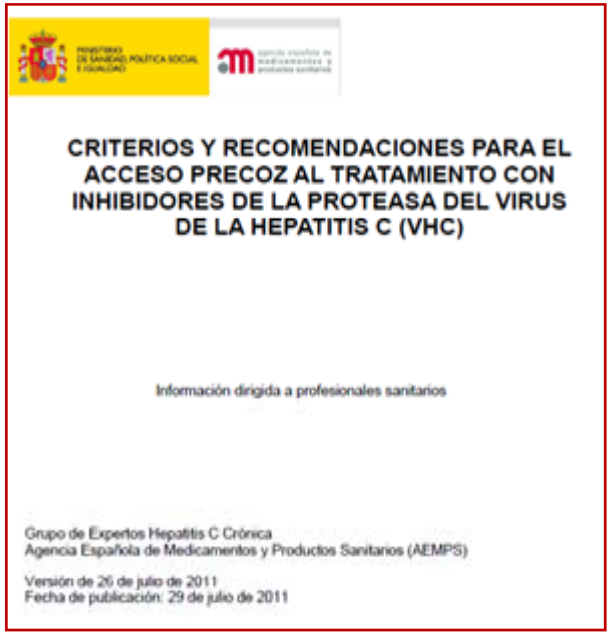
2. **ESTRATEGIA TERAPÉUTICA RECOMENDADA PARA EL USO DE INHIBIDORES DE LA PROTEASA PARA EL TRATAMIENTO DE LA HEPATITIS CRÓNICA C (VHC) EN PACIENTES MONOINFECTADOS EN EL ÁMBITO DEL SISTEMA NACIONAL DE SALUD**

- Algoritmo recomendado de tratamiento
- Anexo de priorización
  - F3-F4
  - Excepciones

EFICACIA Y SEGURIDAD DE LA TRIPLE TERAPIA CON PEGINTERFERON, RIBAVIRINA Y BOCEPREVIR EN USO COMPASIVO EN PACIENTES CON HEPATITIS C GENOTIPO 1 CON FIBROSIS AVANZADA: ANALISIS INTERMEDIO A LAS 12 SEMANAS

AUTORIZACION POR PARTE DE LA EMEA

BOCEPREVIR 27/07/2011
TELAPREVIR 30/09/2011



CRITERIOS Y RECOMENDACIONES PARA EL ACCESO PRECOZ AL TRATAMIENTO CON INHIBIDORES DE LA PROTEASA DEL VIRUS DE LA HEPATITIS C (VHC)

Información dirigida a profesionales sanitarios

Grupo de Expertos Hepatitis C Crónica
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)

Versión de 26 de julio de 2011
Fecha de publicación: 29 de julio de 2011

30/12/2011

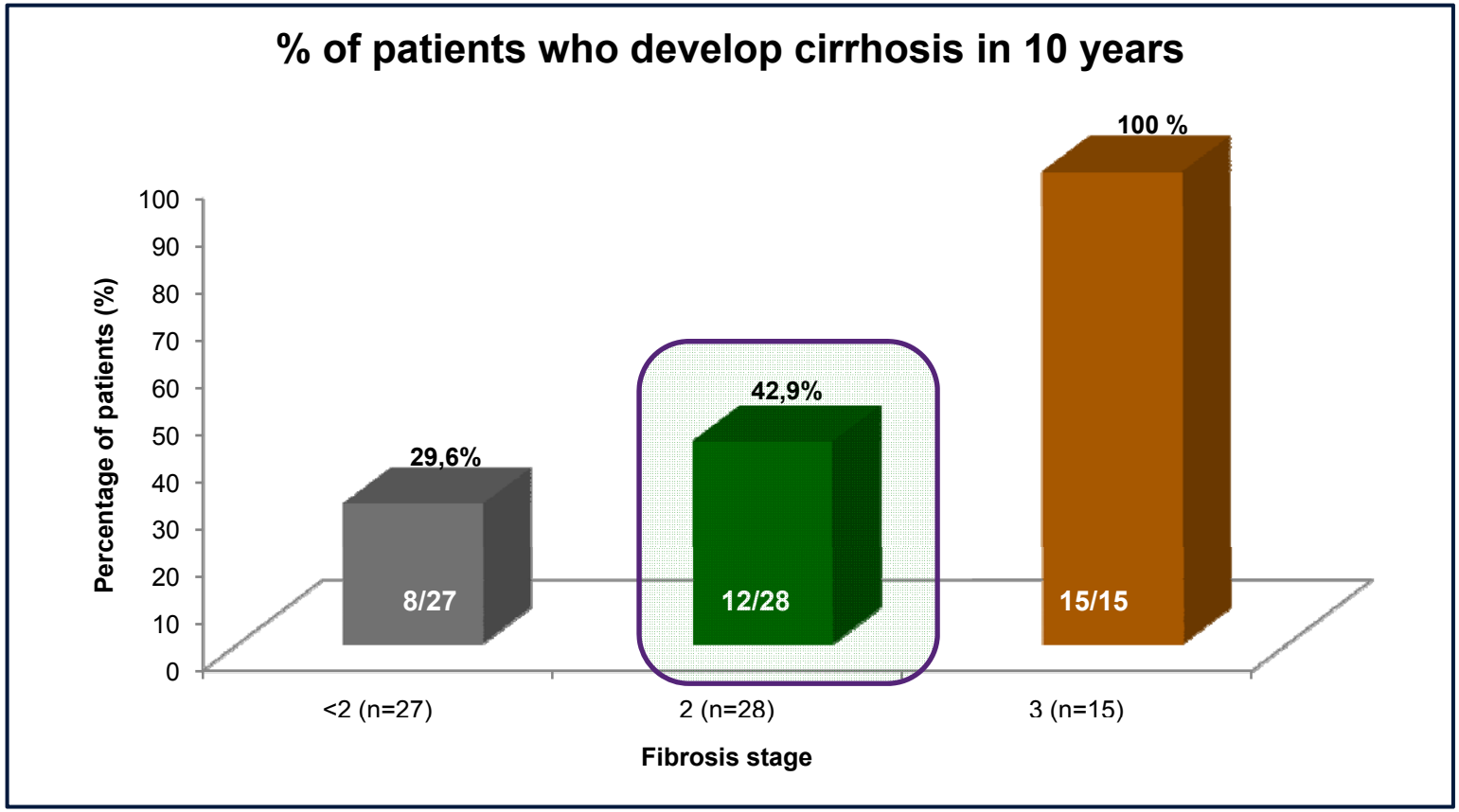
COMERCIALIZACION

Calleja JL et al EASL 2013

Actualizacion Mayo 2013

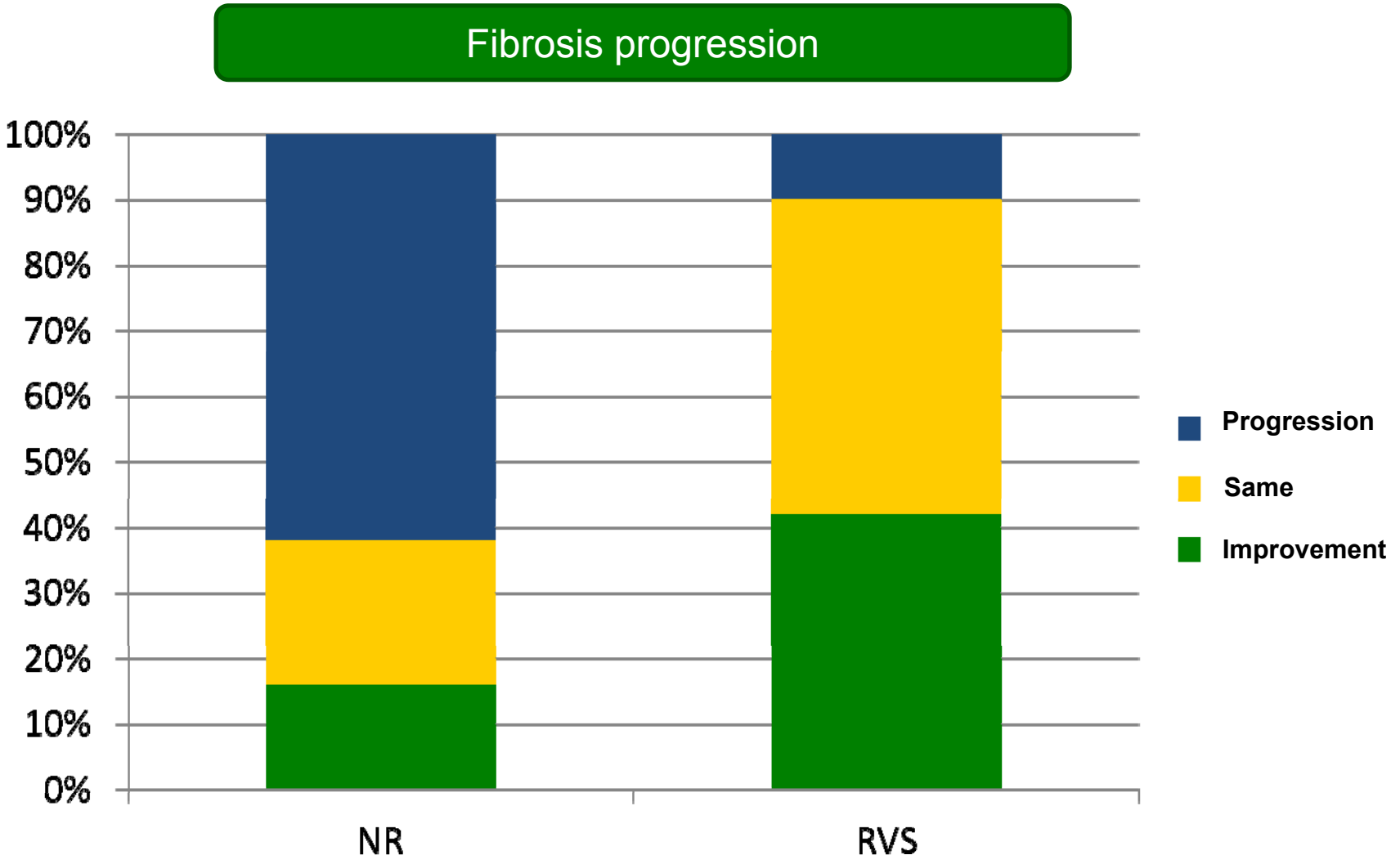
- Pacientes F2
- Boceprevir : Semana 8
- Telaprevir: dosis cada 12 horas
- Pacientes F4 avanzados

Progression of HCV disease



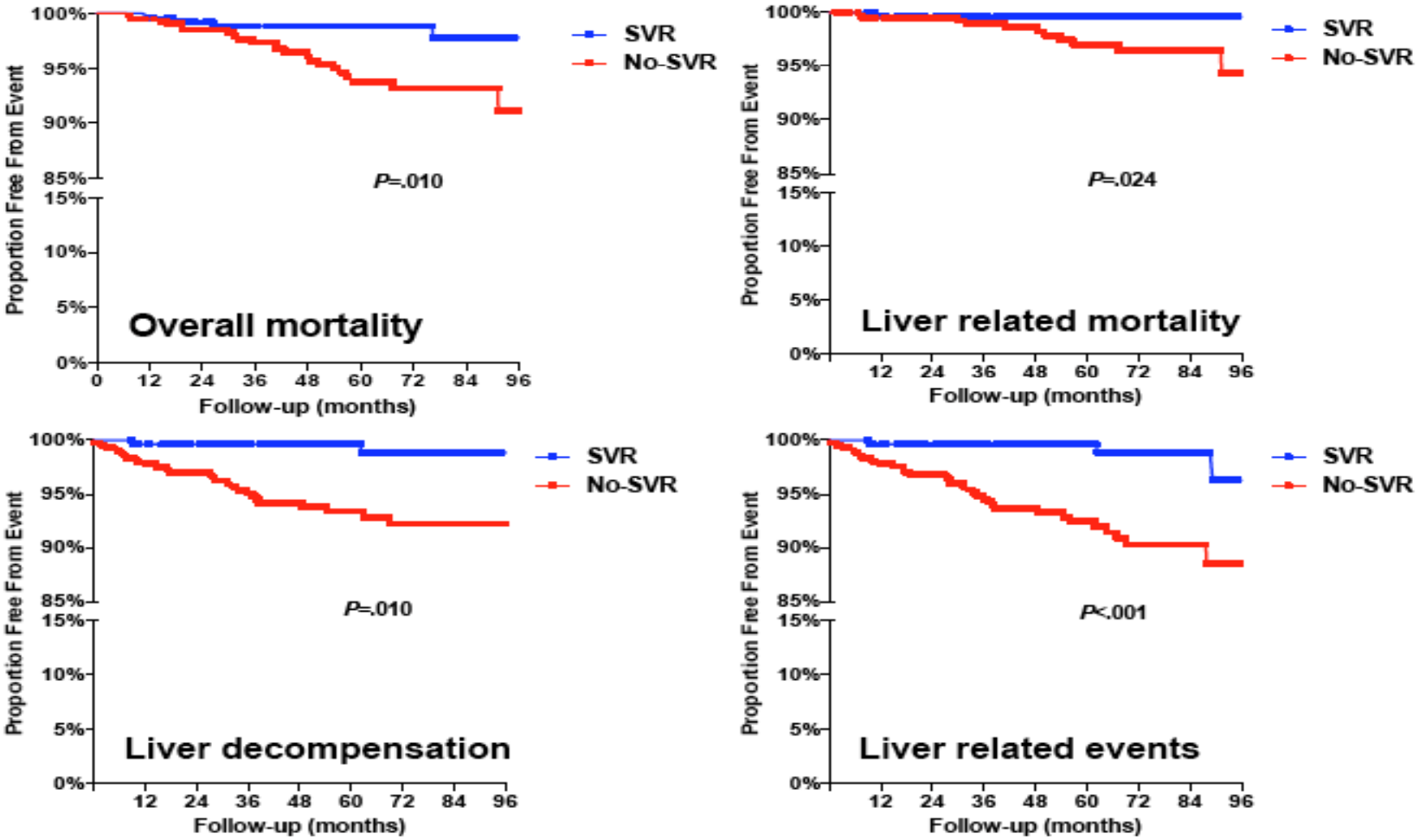
Yano M, et al. Hepatology. 1996;23:1334-1340

Impact of SVR in the progression in patients with F2 fibrosis



Cañete N. et al. Gastroenterología y Hepatología 2010. Vol 36 Esp. Congr. 1. P-105 (pags 76)

Impact of SVR in the development of clinical events in F2



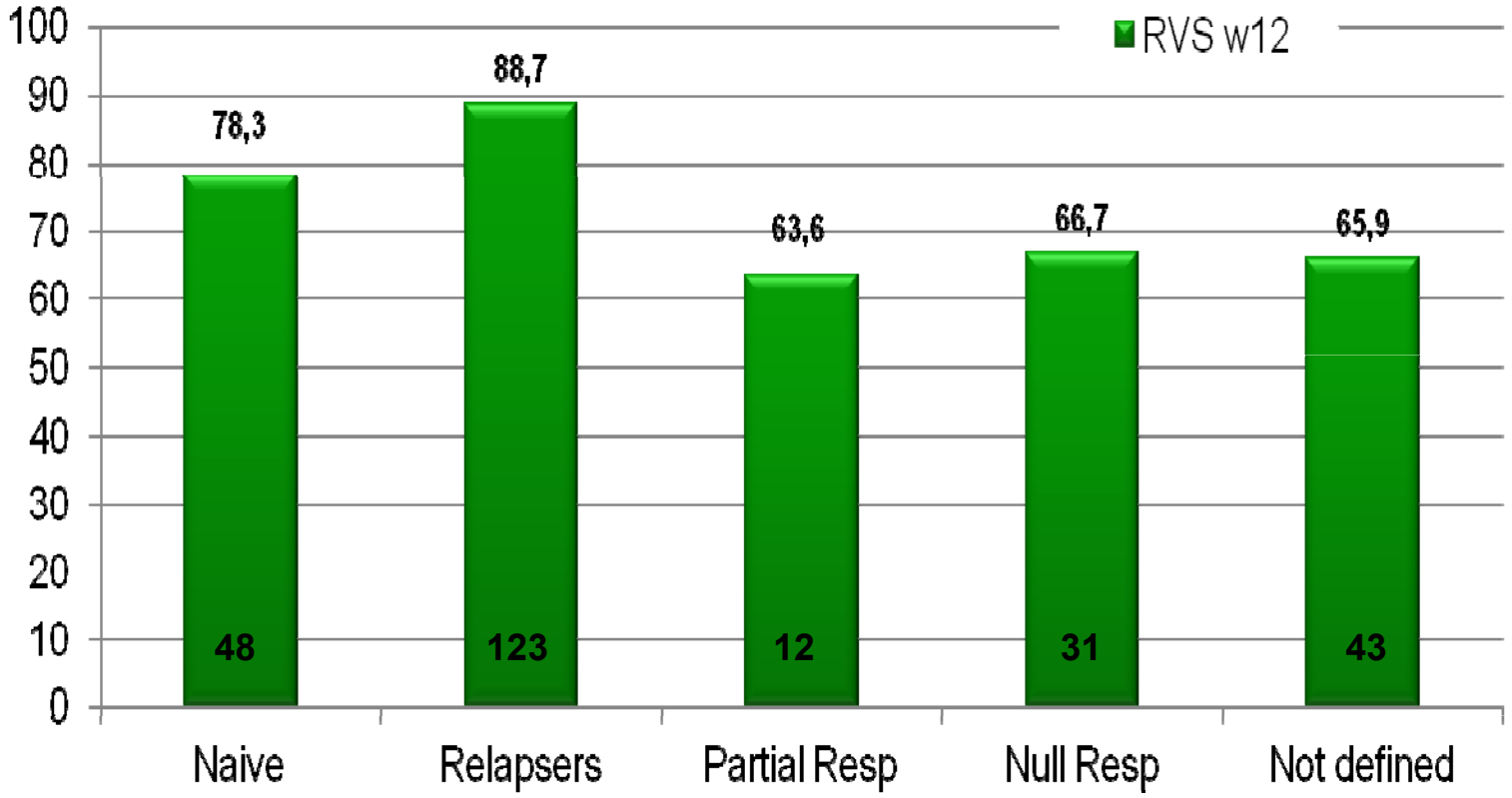
Berenguer J, Zamora FX, Díez C, et al. Hepatitis C eradication reduces liver decompensation, HIV progression, and death in HIV/HCV-coinfected patients with non-advanced liver fibrosis. 53rd ICAAC. September 10-13, 2013. Denver. Abstract H-1527.

Baseline Characteristics

	F2 (n= 214)	F3/F4 (n= 368)
Male (n, %)	114 (67)	245 (66,7)
Mean Age (SD), range	54,2 (9,7); 25 - 74	55,3 (8,5); 24 - 74
BMI (Kg/m^2), mean (SD), range	26,3 (3,9); 19 - 45	27,3 (4,6); 19 - 54
Genotipe VHC		
Ia	41 (19)	75 (20,3)
Ib	154 (71,8)	242 (65,8)
Mixed (n, %)	19 (9)	51 (13,8)
Viral load >800.000 UI/l (n, %)	147 (68,6)	288 (78,4)
Viral load (log 10)	6,06 (0,66)	6,2 (0,7)
IL28 Genotype		
CC	30 (14)	63 (17,7)
CT	111 (51,8)	176 (47,7)
TT	30 (14)	54 (14,4)
ND (n, %)	43 (20)	73 (19,8)

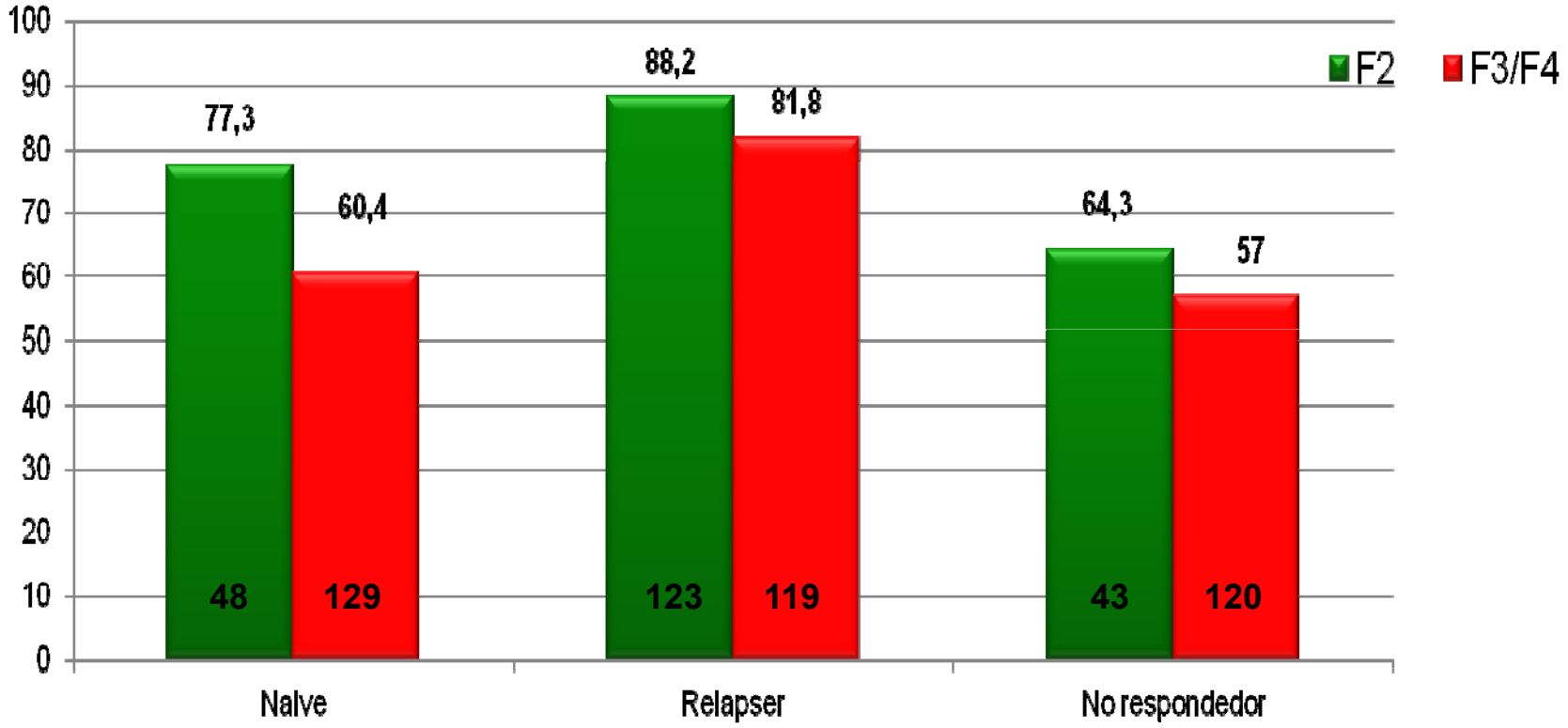
Crespo J et al AEEH 2014

SVR in F2 Patients



Crespo J et al AEEH 2014

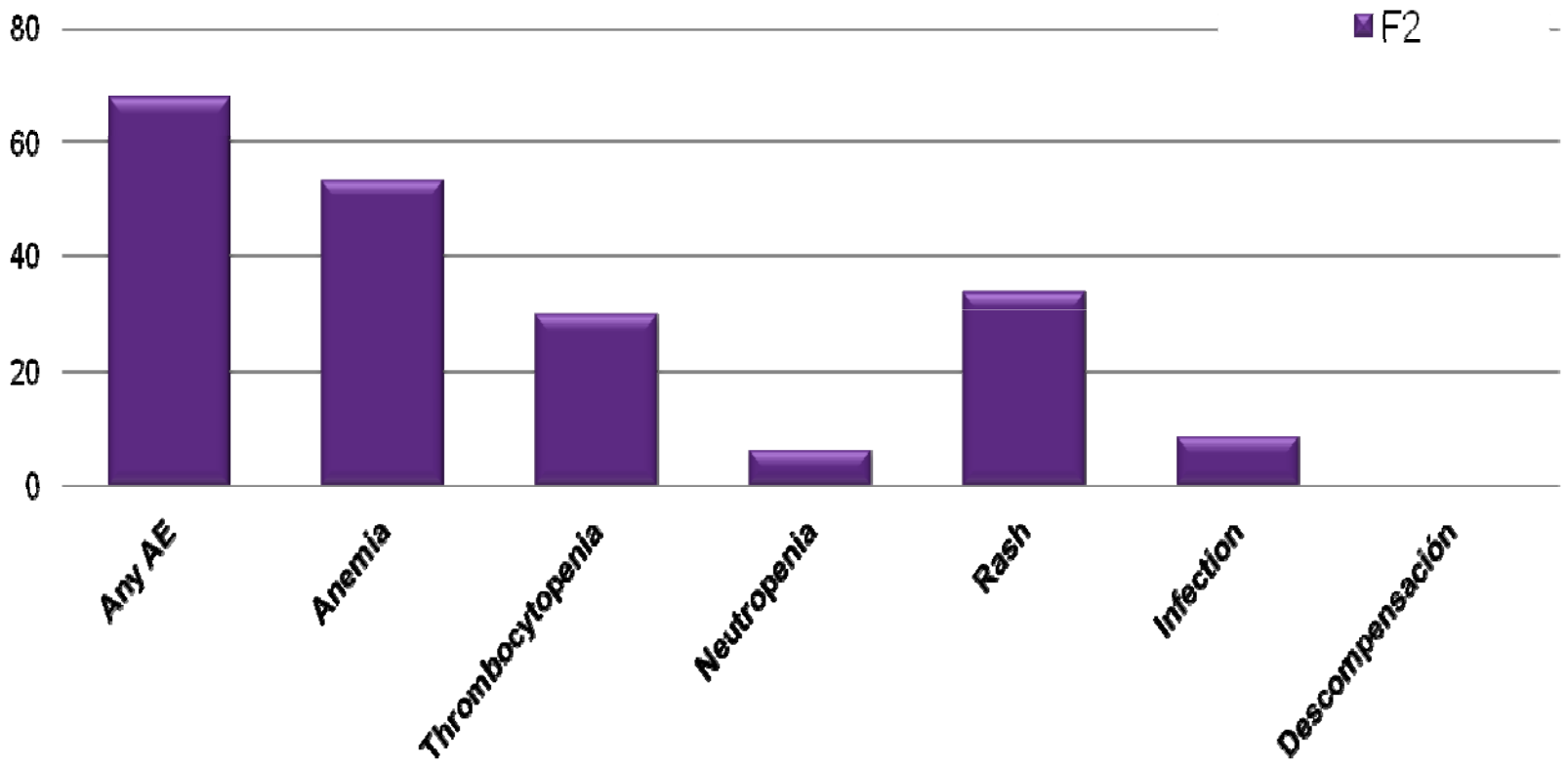
SVR F2 vs F3-F4



HR: 1.139 (1.036 – 1.252); p= 0,006

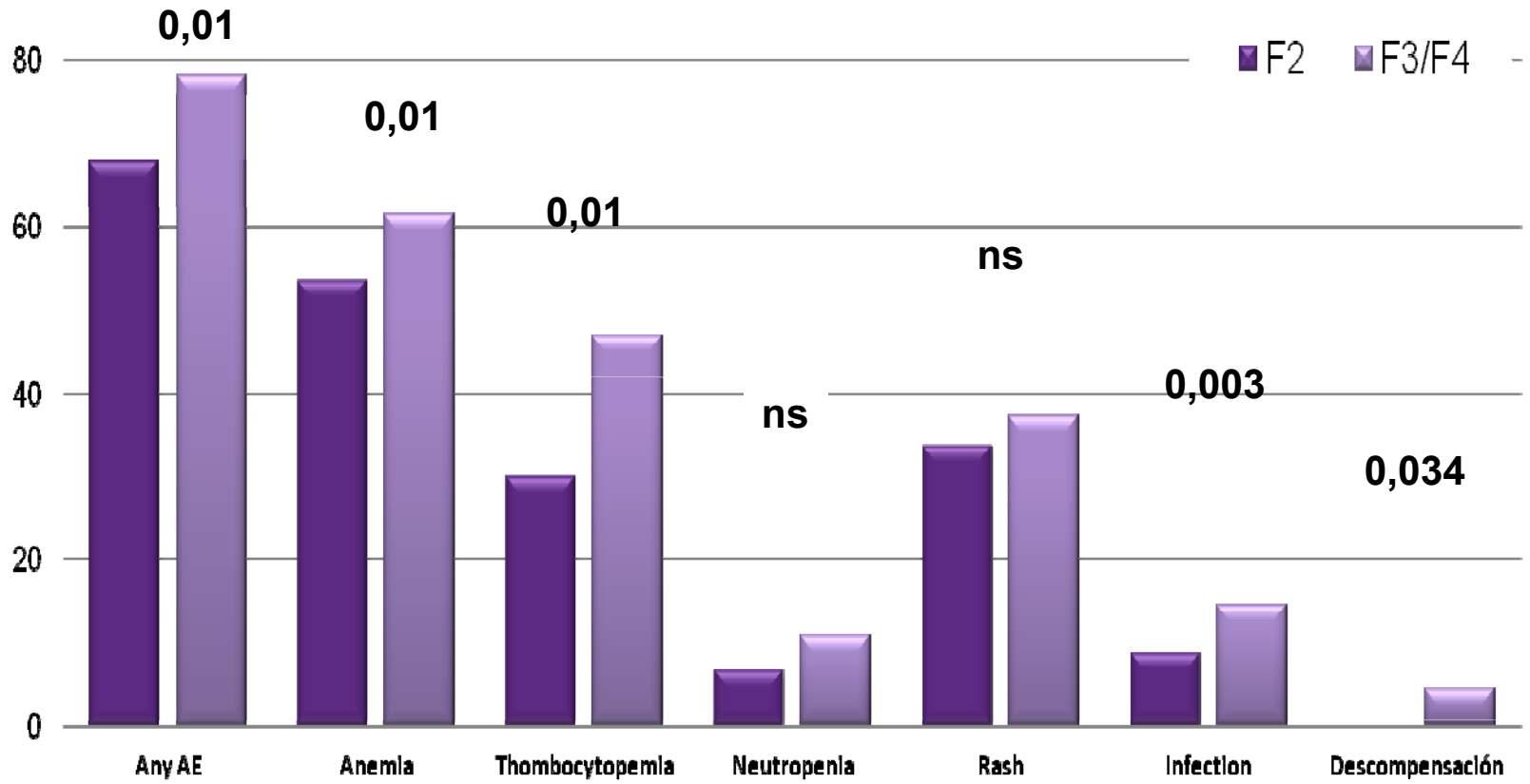
Crespo J et al AEEH 2014

Adverse Events in F2 Patients



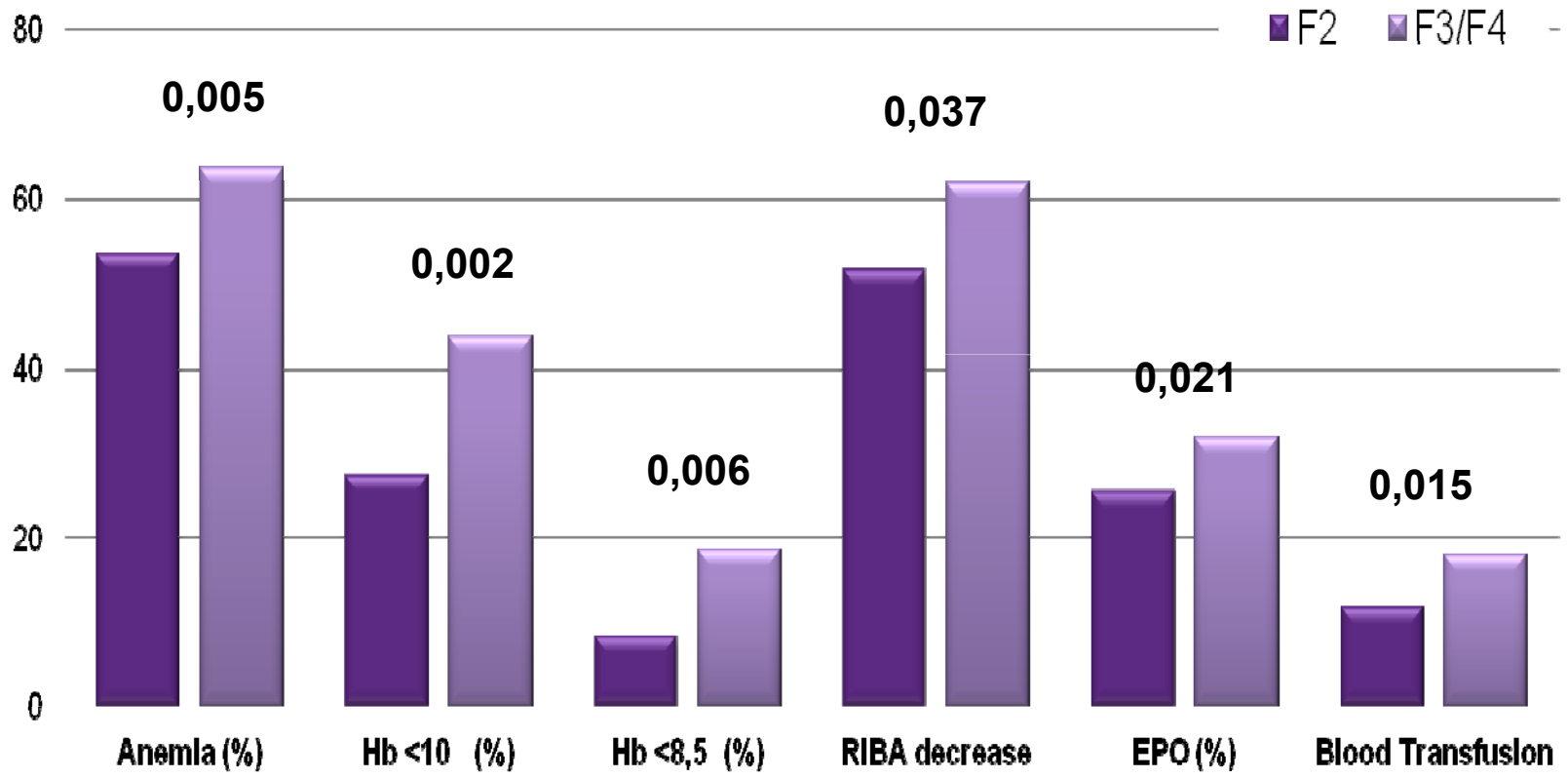
Crespo J et al AEEH 2014

Adverse Events F2 vs F3-F4



Crespo J et al AEEH 2014

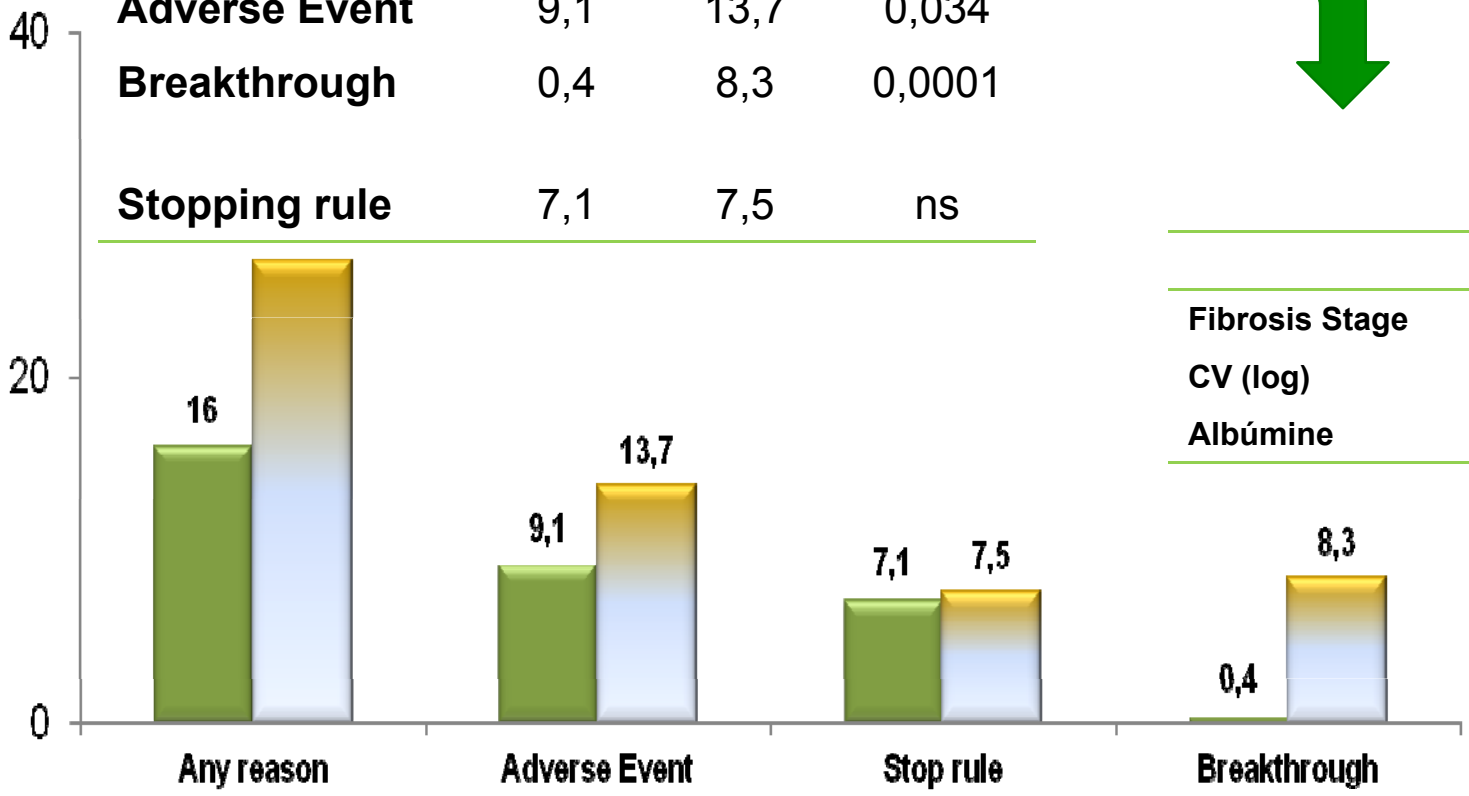
Adverse Events F2 vs F3-F4



Crespo J et al AEEH 2014

Treatment Failure in F2

	F2	F3/F4	p
Adverse Event	9,1	13,7	0,034
Breakthrough	0,4	8,3	0,0001
Stopping rule	7,1	7,5	ns

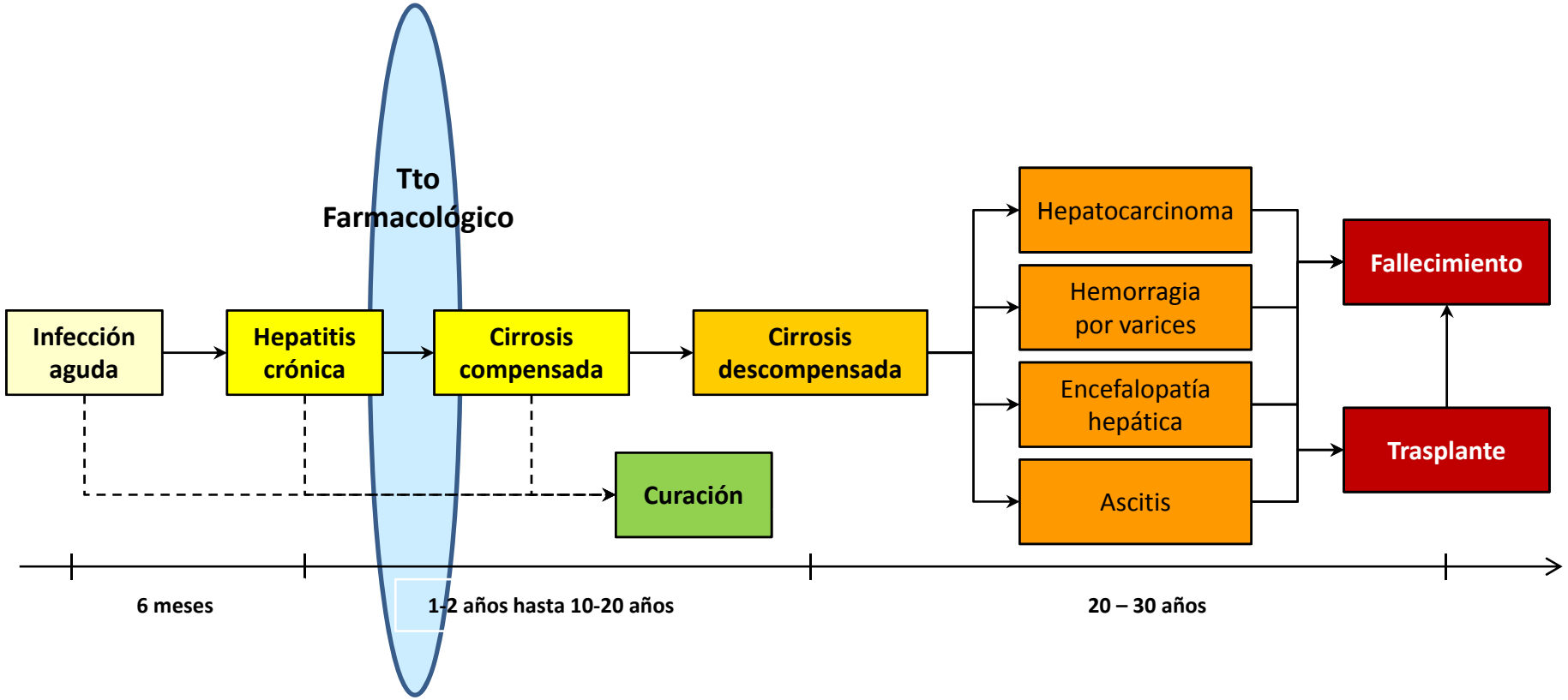


	p
Fibrosis Stage	0,0001
CV (log)	0,053
Albúmine	0,05

Crespo J et al AEEH 2014

Avances en el tratamiento de la Hepatitis C en el paciente monoinfectado.

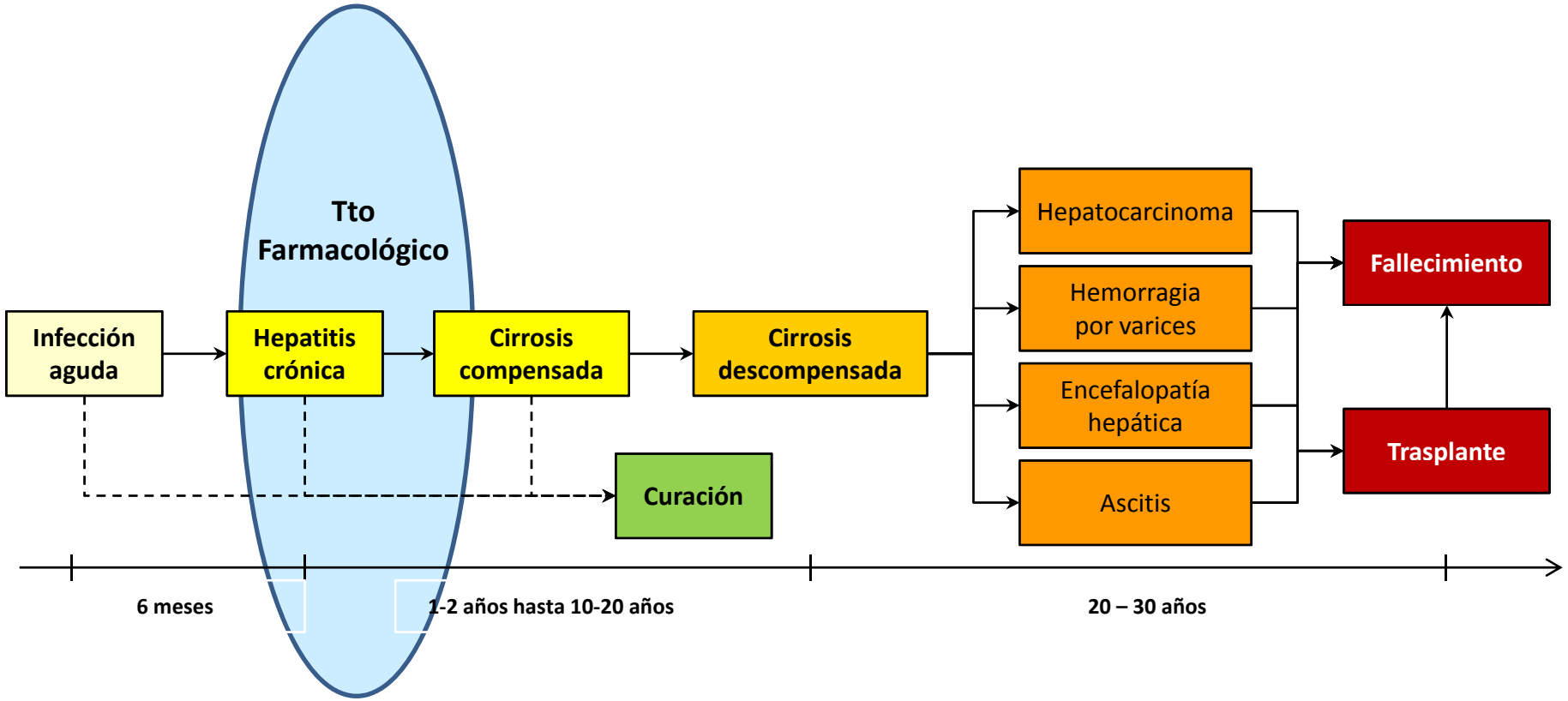
Ventana terapéutica.



Hemos disminuido mucho la ventana terapéutica.

Avances en el tratamiento de la Hepatitis C en el paciente monoinfectado.

Ventana terapéutica.

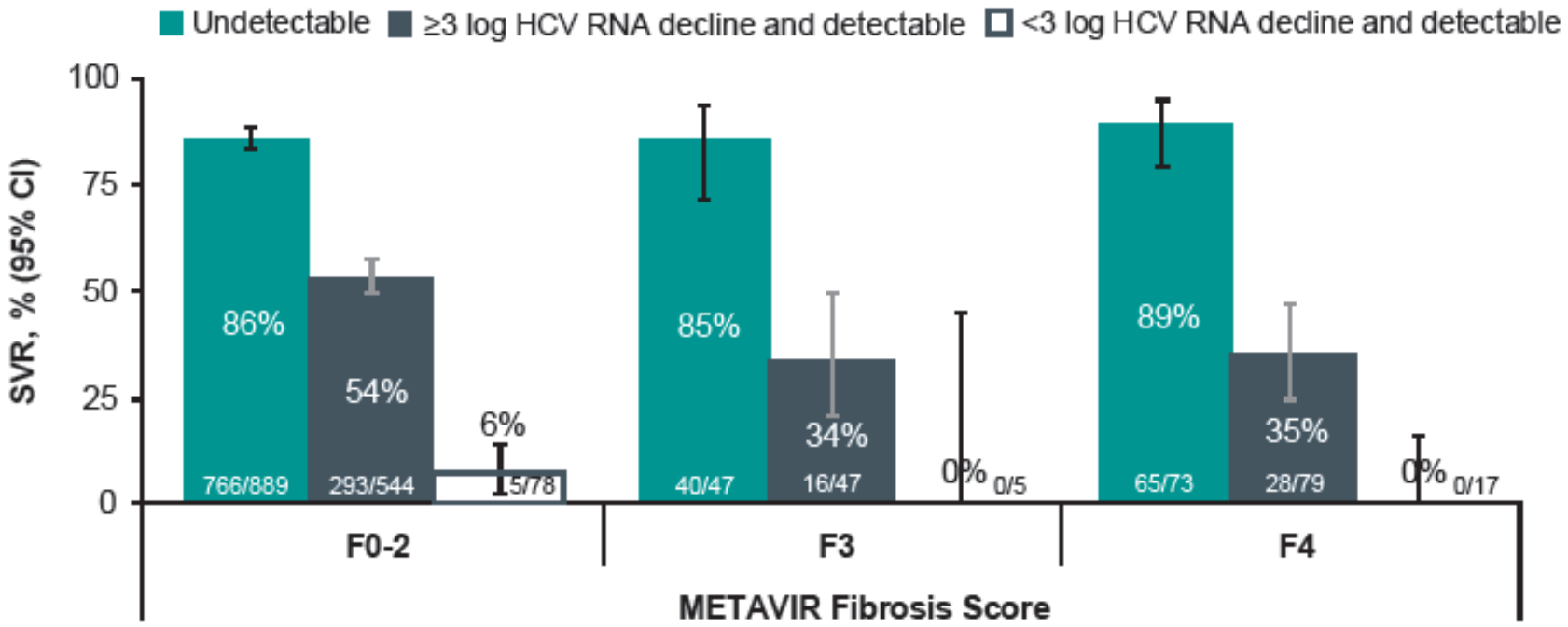


Actualizacion Mayo 2013

- Pacientes F2
- Boceprevir : Semana 8
- Telaprevir: dosis cada 12 horas
- Pacientes F4 avanzados

SVR in advanced patients with Boceprevir: results from the meta-analysis

SVR according to the response by week 8

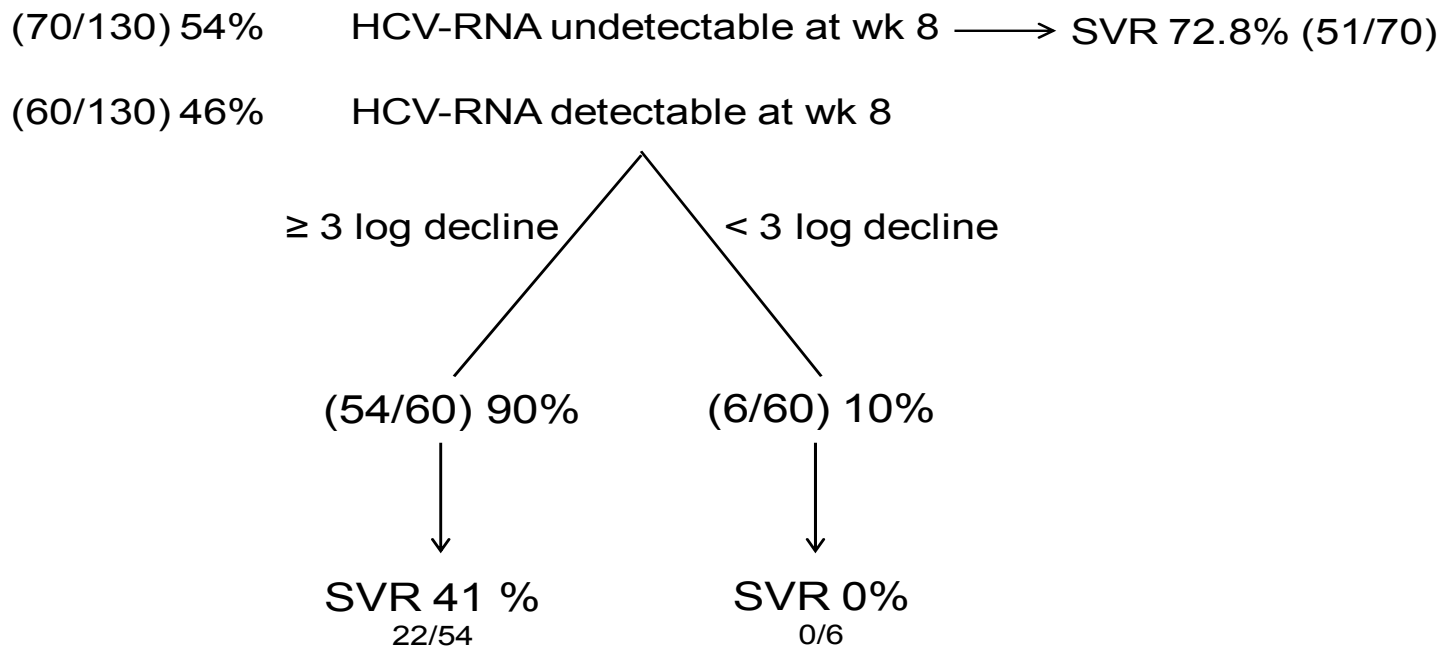


No F3 (0/5) or F4 (0/17) patients with < 3 $\log_{10}$ decline and detectable HCV-RNA at TW8 achieved SVR

Vierling et al, EASL 2013, #1430

EFFICACY AND SAFETY OF TRIPLE THERAPY WITH PEGINTERFERON, RIBAVIRIN, AND BOCEPREVIR WITHIN EARLY ACCESS PROGRAM IN SPANISH PATIENTS WITH HEPATITIS C GENOTYPE 1 WITH SEVERE FIBROSIS. SVR12 ANALISYS

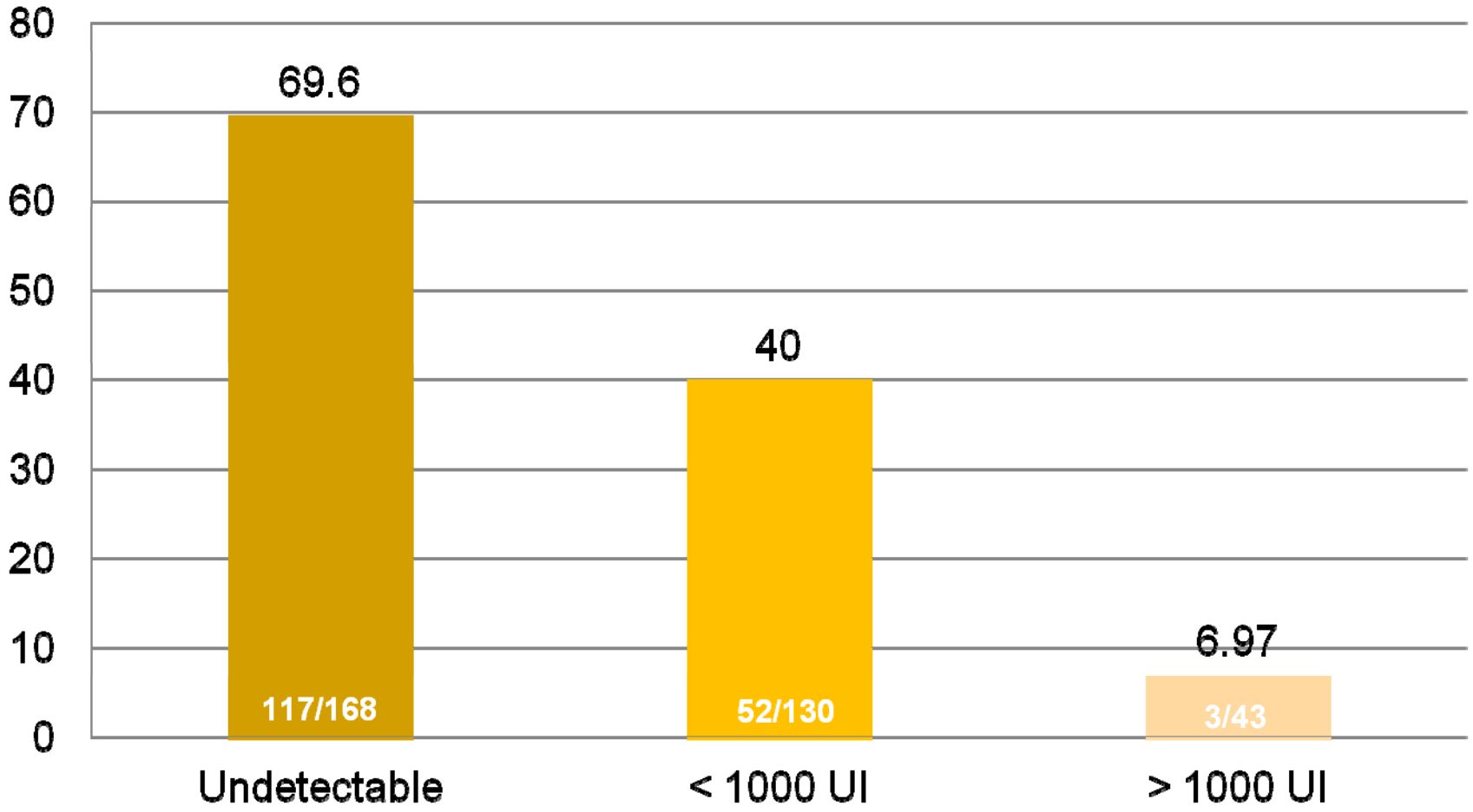
VIRAL LOAD WEEK 8



NPP Spain, Total patients 170, Premature discontinuation (before 8 w) 32 pts ; No data available:8 pts; **data available in 130 pts**

Calleja et al AEEH 2014

Overall SVR12 according to treatment week 8 virologic response



Bruno et al EASL 2014

Multivariate logistic regression analysis Predictors of Treatment Failure (NO SVR) in 369 F3/F4 patients receiving BOC

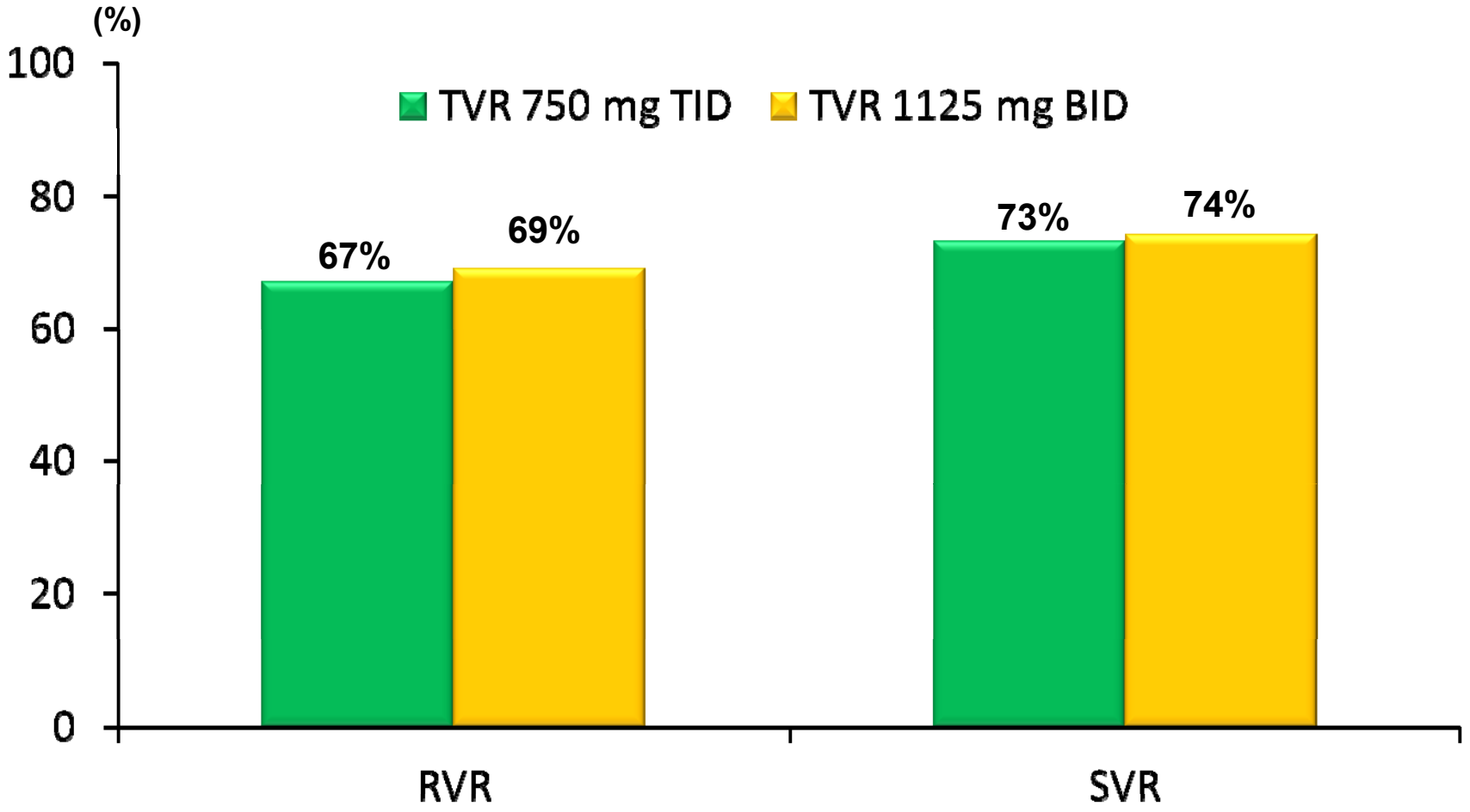
Variable	Reference	Univariate RR (95% CI)	Multivariate RR (95% CI)	p-value
TW8 <1000 IU/mL	Undetectable	**3.44 (2.13-5.57)**	**3.77 (2.24-6.34)**	**<0.0001**
TW8 >1000 ≥3 log decline	Undetectable	**52.8 (6.94-401.)**	**57.7 (6.97-478.)**	**0.0002**
TW8 >1000 <3 log decline	Undetectable	**19.5 (4.34-87.5)**	**24.3 (4.73-124.)**	**0.0001**
TW4 <1 log decline	≥1 log decline	**1.84 (1.14-2.97)**	1.12 (0.63-2.00)	0.71
Male	Female	0.91 (0.61-1.38)	-	
Age ≥60 years	<60 years	1.11 (0.71-1.73)	-	
Metavir F4	F3	**1.53 (1.00-2.34)**	0.99 (0.59-1.65)	0.97
Varices	No varices	1.28 (0.72-2.28)	-	
Varices not evaluated	No varices	0.84 (0.53-1.32)	-	
HCV genotype 1a	1b	1.20 (0.72-2.00)	-	
Prior null	Prior relapser	**2.55 (1.57-4.13)**	**1.79 (1.01-3.17)**	**0.046**
Prior partial	Prior relapser	1.58 (0.92-2.73)	1.60 (0.85-3.01)	0.15
Albumin <3.5	≥3.5	**17.0 (2.22-130.)**	**15.6 (1.84-133.)**	**0.01**
PLT <100,000	≥100,000	**3.72 (1.72-8.08)**	**4.31 (1.78-10.5)**	**0.001**
Baseline viral load >800,000	≤800,000	1.10 (0.71-1.71)	-	

Bruno et al EASL 2014

Actualizacion Mayo 2013

- Pacientes F2
- Boceprevir : Semana 8
- Telaprevir: dosis cada 12 horas
- Pacientes F4 avanzados

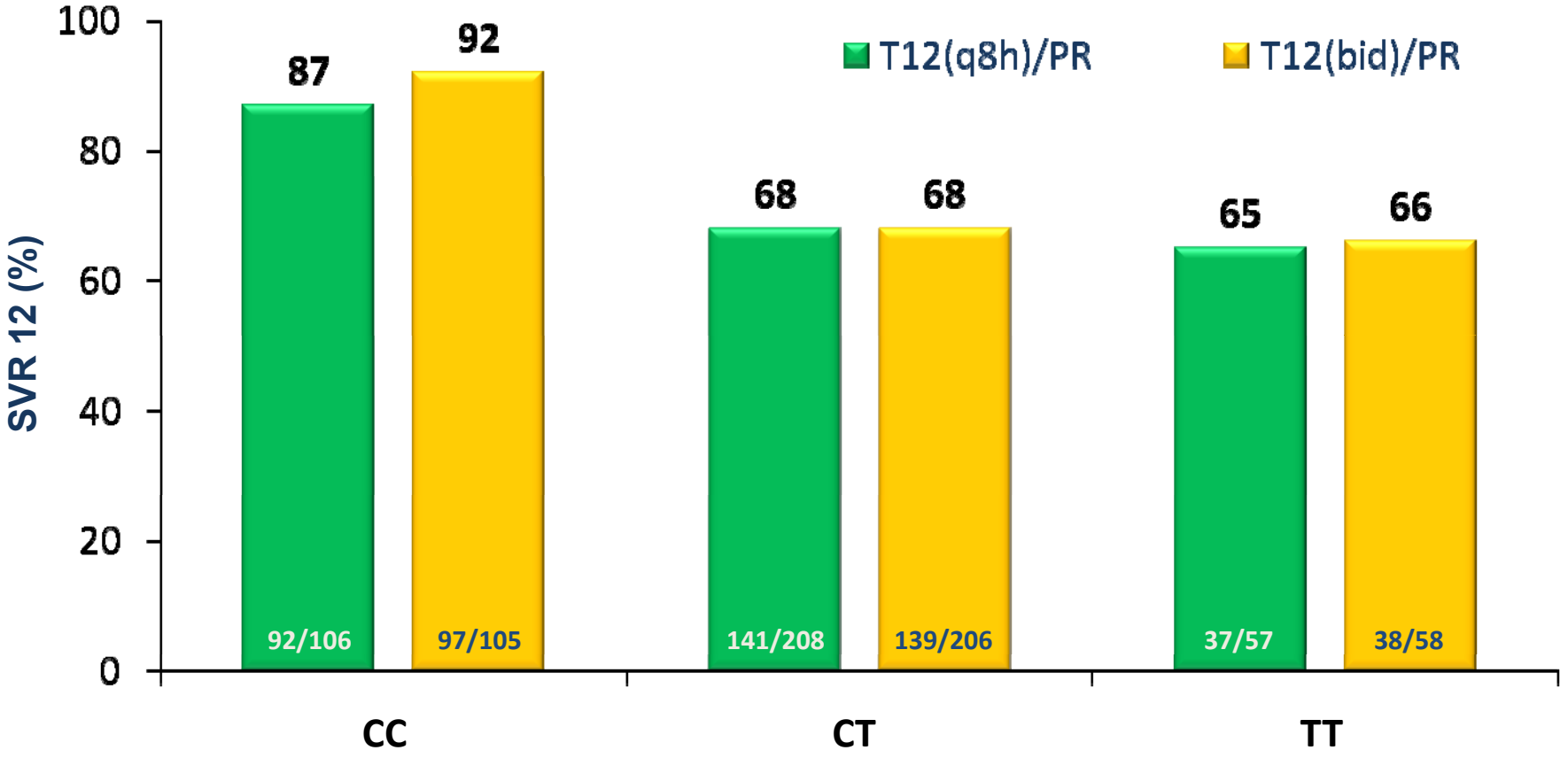
EFICACIA TELAPREVIR 2 VECES AL DÍA



- T12(bid)/PR fue NO INFERIOR a T12(q8h)/PR en el punto de evaluación de SVR12
  - Diferencia (95% IC): 1.5% (–4.9%, 12%)

Buti,M et al. AASLD ABSTRACTS HEPATOLOGY, October, 2012

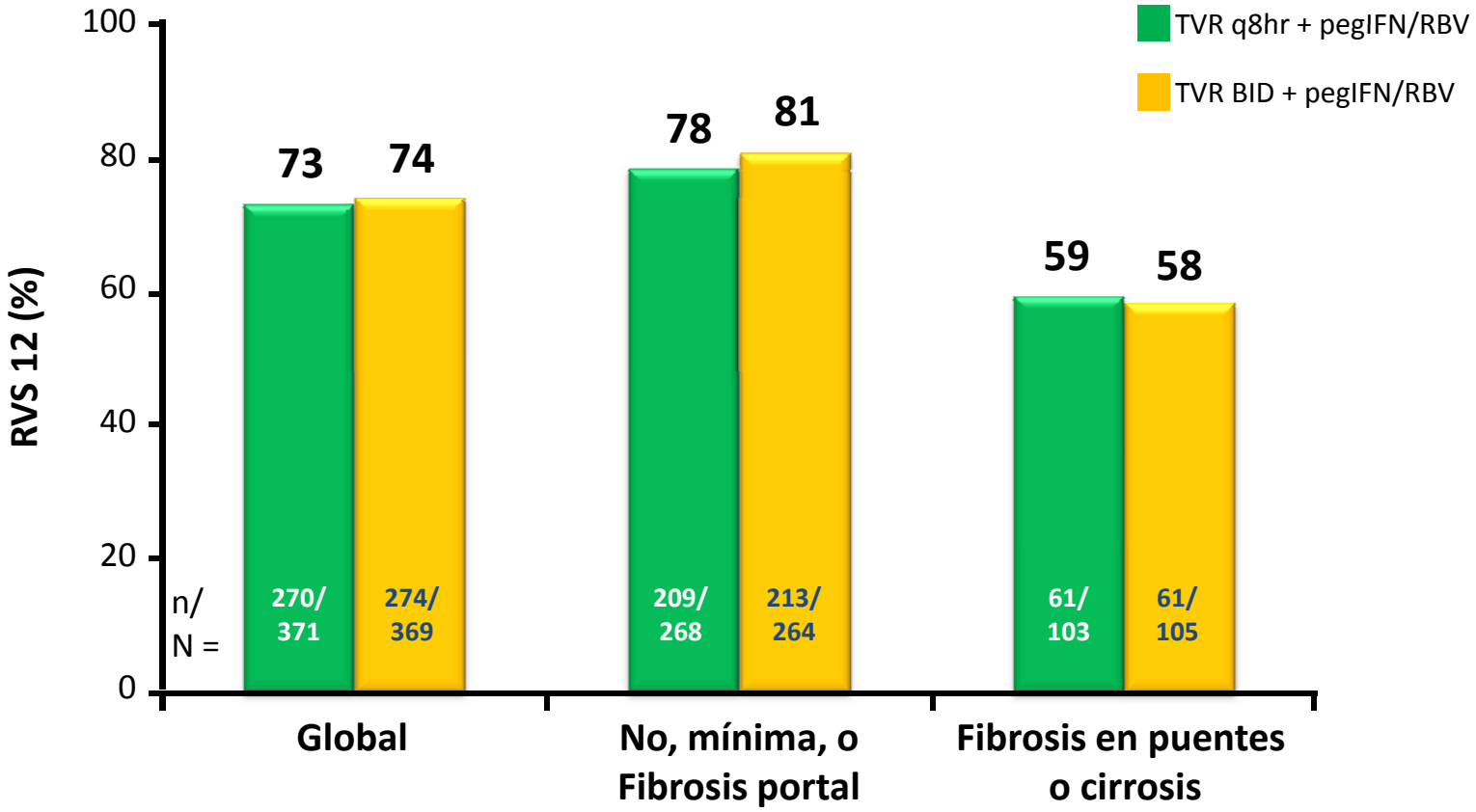
EFICACIA TELAPREVIR 2 VECES AL DÍA SEGÚN GENOTIPO DE LA IL28B



Full analysis population

Buti,M et al. AASLD ABSTRACTS HEPATOLOGY, October, 2012

EFICACIA TELAPREVIR 2 VECES AL DÍA SEGÚN ESTADIO DE FIBROSIS



Buti,M et al. AASLD ABSTRACTS HEPATOLOGY, October, 2012

Actualizacion Mayo 2013

- Pacientes F2
- Boceprevir : Semana 8
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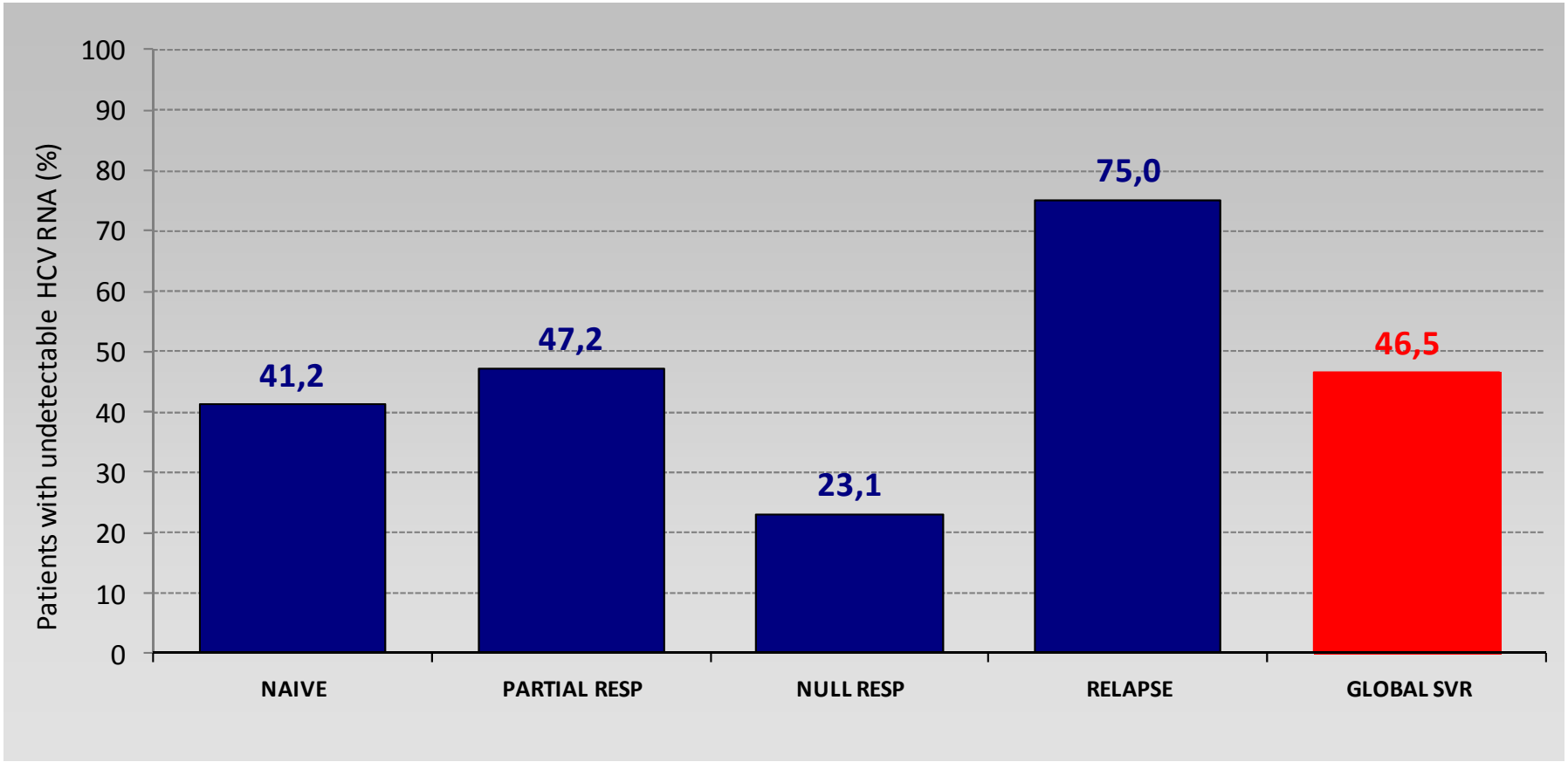
- Pacientes F4 avanzados

BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Characteristics	Subjects (n=170)
Male gender. n (%)	116 (68.2)
Mean age (range). years	53 (29-76)
HCV Genotype 1a/1b. n (%)	42/128 (25/75)
Baseline RNA- HCV (Mean. log10 UI/mL)	6.2 log (0.7)
>800.000 n (%)	120 (70.6)
F4. n (%)	134 (78.8)
Esophageal varices. n (%)	65 (38.2)
Naïve	34 (20.0)
Non- responders. n (%)	
Relapser	48 (35.3)
Partial responder	36 (26.5)
Null-responder	52 (38.2)

Calleja et al AEEH 2014

SVRw12. Intent to Treat Analysis (n=170)

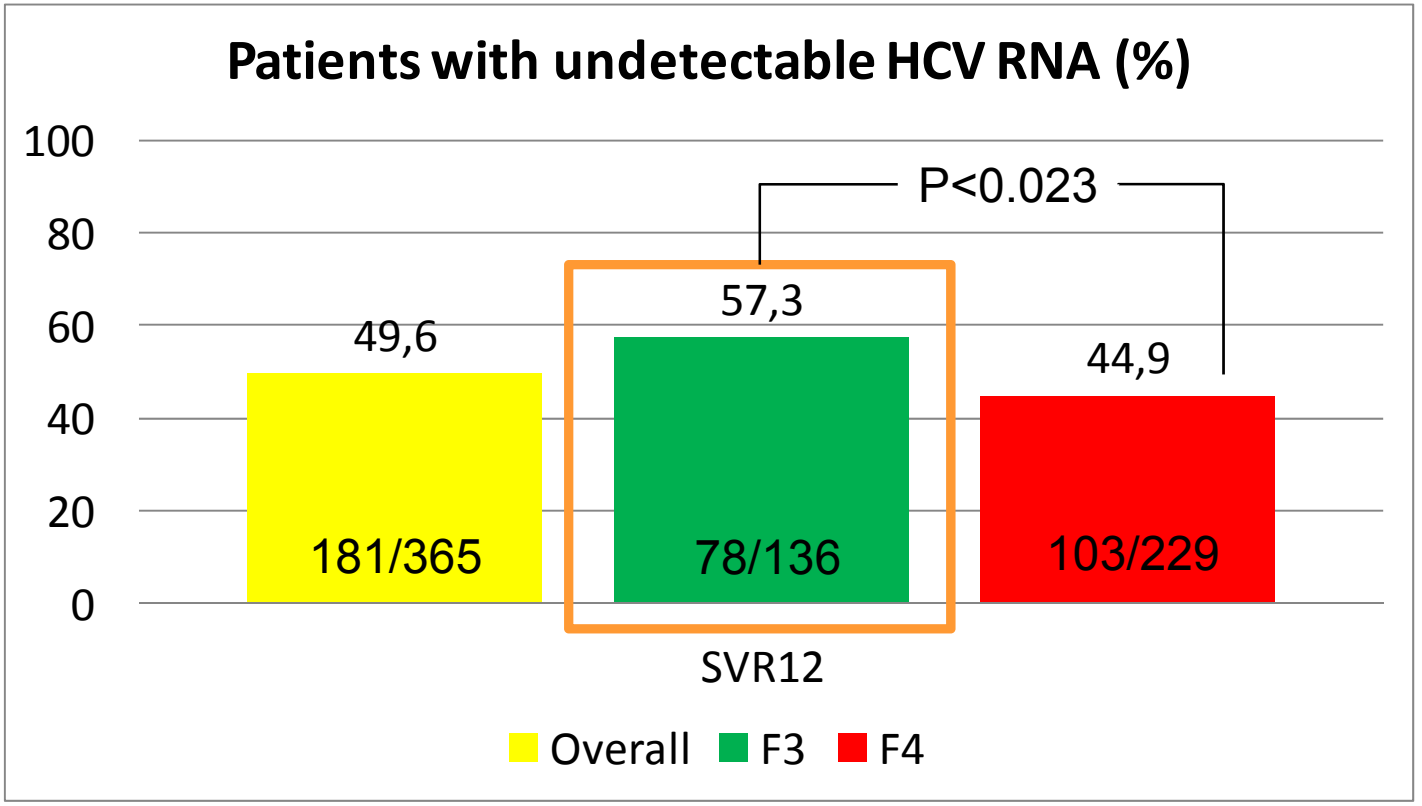


Calleja et al AEEH 2014

Factors related to Treatment Failure		n=79 (46.5%)					
		Univariate analisys			Multivariate analysis		
		OR	95 % CI	p value	OR	95 % CI	p value
Age (years)							
	> 70	1.919	1.658-2.222	0.05			
Platelet count /mm3							
	<100000	0.289	0.127-0.660	0.002			
	<90000	0.305	0.122-0.759	0.008			
	<80000	0.294	0.103-0.839	0.017			
	Continuous variable		(-45094.6- -325.672)	0.047			
Serum Albumin (g/dl)							
	<3.5	0.214	0.045-0.976	0.036	12,226	0.68-328.67	0.08
			(-0.314- -0.020)	0.026			
AST			9.419-44.519	0.003			
RESPONSE TO PREV TX							
	Relapse/naive	4.282	1.660-11.021	0.001			
	Relaose/ Partial	3.353	1.331-8.453	0.006	13.264	3.70--47.51	0.0001
	Relaose/ Null	10.001	3.993-25.031	0.0001			
LEAD IN RESPONSE							
	Respuesta/no respuesta	4.434	2.001-9.820	0.0001	4.907	0.03-0.715	0.018
ILB28							
	CC/ no CC	4.340	1.102-17.243	0.027			

Italy - Spain NPP SVR12 rates by ITT Analysis
Treatment experienced patients

N= 416 patients



Bruno et al EASL 2014

Patients. n (% patients with at least one event)	Week 12 after the planned end of treatment (n=170)
Serious adverse events (SAEs)	62 (36.5%)
Premature discontinuation	62 (36.5%)
Due to SAEs	15 (8.8%)
Discontinuing patient care	7 (4.1%)
Virological failure	40 (23.5%)
Death	2 (1.18%)
Septic shock. Multi-organ failure secondary to pneumonia	
Dose modification (PegIFN)	40 (23.5%)
Infection/Infection Grade 3-4	51 (30.0%)/17 (10.0%)
Liver decompensation (Grade 3/4)	10 (5.9%)

Calleja et al AEEH 2014

Patients. n (% patients with at least one event)	Week 12 after the planned end of treatment (n=170)
Anaemia	
Hb <10.0 g/dL	81 (47.6%)
Hb <8.0 g/dL	8 (4.7%)
EPO use	46 (27.1%)
Blood transfusion	12 (7.6%)
Ribavirin dose adjustment	84 (49.4%)
Neutropenia	
N < 1.000/mm3	98 (57.6%)
N < 500/mm3	12 (7.1%)
Use G-CSF	6 (3.5%)
Thrombopenia/mm3	
platelets <50.000	44 (25.9%)
platelets <25.000	7 (4.1%)

Calleja et al AEEH 2014

EFFICACY AND SAFETY OF TRIPLE THERAPY WITH PEGINTERFERON, RIBAVIRIN, AND BOCEPREVIR WITHIN EARLY ACCESS PROGRAM IN SPANISH PATIENTS WITH HEPATITIS C GENOTYPE 1 WITH SEVERE FIBROSIS. SVRw12 ANALISYS

Factors related to SAEs		n=62 (36.5%)					
		Univariate analisys			Multivariate analysis		
		OR	95 % CI	p value	OR	95 % CI	p value
Age (years)							
	Variable continua		1.105-6.543	0.005			
Platelet count /mm3							
	Variable continua		(-44.81- -2543.65)	0.028			
Serum Albumin (g/dl)							
	<3.5	6.405	1.638- 25.050	0.003	5.208	1.294-20.958	0.020
	Variable continua		(-0.3654- -0.0443)	0.013			
Hemoglobin level (g/dl) (ABNORMAL)							
	<12 (female) <13 (male)	2.862	2.326-3.522	0.008			

Calleja et al AEEH 2014

EFFICACY AND SAFETY OF TRIPLE THERAPY WITH PEGINTERFERON, RIBAVIRIN, AND BOCEPREVIR WITHIN EARLY ACCESS PROGRAM IN SPANISH PATIENTS WITH HEPATITIS C GENOTYPE 1 WITH SEVERE FIBROSIS. SVRw12 ANALISYS

Factors related to Infections grade III/IV		n=17 (10.0%)					
		Univariate analisys			Multivariate analysis		
		OR	95 % CI	p value	OR	95 % CI	p value
Serum Albumin (g/dl)							
	<3.5	6.750	1.667- 37.336	0.003	5.980	1.35-26.37	0.018
	Variable continua		0. 502- 0.544	0.019			
Bilirubin (mg/dl)							
	>2	6.905	1.063.44.862	0.021	19.127	1.38-264.4	0.028
Hemoglobin level (g/dl) (continua)			0.018- 1.501	0.045			

Calleja et al AEEH 2014

Italy- Spain NPP Safety profile

Adverse event	N (%) at anytime during TW4-TW48
Death	3 (0.7) TW6, TW12,TW28
Sepsis, MOF	3 (0.7)
Infections	70 (17.4)
Hepatic decompensation	13 (3.2)
Anemia Grade 2-3 (8,5 < Hb < 10 g/dL) Grade 4 (Hb < 8,5 g/dL)	 139 (34.6) 41 (10.2)
Neutropenia Grade 3 (500 < N < 750) Grade 4 (N < 500)	 91 (22.6) 50 (12.4)
Thrombocytopenia Grade 3 (25000< PLT< 50000) Grade 4 (PLT< 25000)	 23 (5.7) 2 (0.5)
Cutaneous AE	68 (16.9)
Cardiovascolar AE	7 (1.7)
Gastrointestinal Disorders	64 (15.9)
EPO	159 (39.5)
Transfusion	31 (7.7)

Bruno et al EASL 2014

SVR12 and severe complications rates according to baseline platelet count and serum albumin*

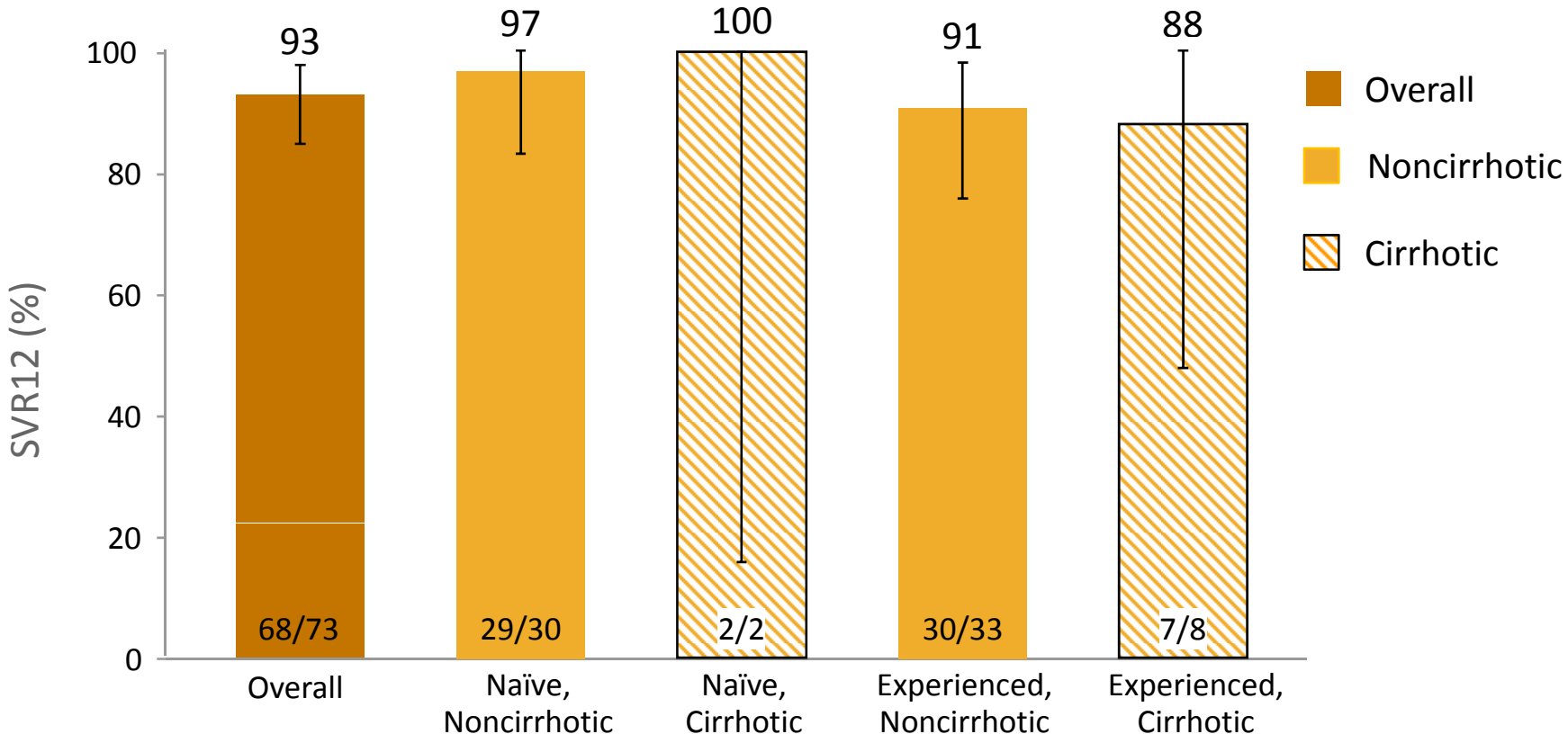
		Platelet count ≤100,000/mm³	Platelet count >100,000/mm³
Albumin <35 g/L	N	37	31
	Complications, n (%)	19 (51.3)	5 (16.1)
	SVR12, n (%)	8 (21.6)	9 (29.0)
Albumin ≥35 g/L	N	74	305
	Complications, n (%)	9 (12.2)	16 (5.2)
	SVR12, n (%)	26 (35.1)	160 (52.5)

*Missing data in 69 patients

Hézode C, et al. Unpublished data

SOF + RBV for 12 Weeks for HCV GT 2

VALENCE Virologic Response and SVR12

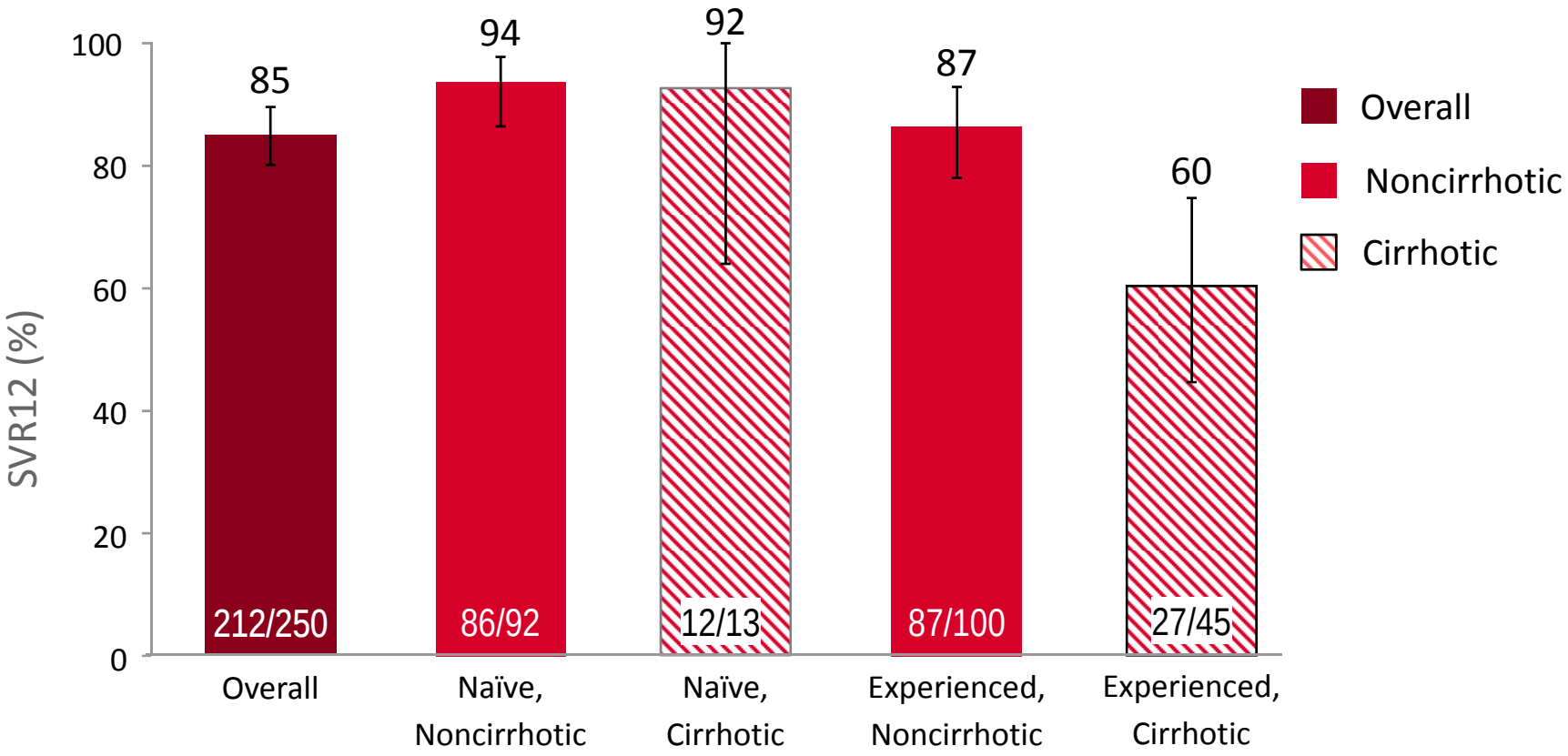


- At Week 4, 100% of patients had HCV RNA below LLOQ
- Confirmed high SVR observed with SOF + RBV for 12 weeks in GT 2 patients
- No S282T mutations were observed by population or deep sequencing

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

SOF + RBV for 24 Weeks for HCV GT 3

VALENCE Virologic Response and SVR12



- At Week 4, 100% of patients had HCV RNA below LLOQ
- High SVR observed with all oral regimen of SOF + RBV for 24 weeks in GT 3 patients
- No S282T mutations were observed by population or deep sequencing

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

SOF + RBV for 12 Weeks for HCV GT 2 and 24 Weeks for GT 3

VALENCE Grade 3 or 4 Laboratory Abnormalities

n (%)	GT 2/3 SOF + RBV 12 wk (n=84)	GT 3 SOF + RBV 24 wk (n=250)
Maximum post-baseline toxicity grade		
Grade 3	16 (19)	43 (17)
Grade 4	1 (1)	2 (< 1)
Hemoglobin	7 (8)	28 (11)
Lymphocytes	1 (1)	5 (2)
Neutrophils	1 (1)	0
Platelets	0	3 (1)
Alanine aminotransferase (ALT)	1 (1)	3 (1)
Aspartate aminotransferase (AST)	1 (1)	0
Lipase	3 (4)	5 (2)
Hyperglycemia	1 (1)	2 (< 1)
Total bilirubin	5 (6)	7 (3)

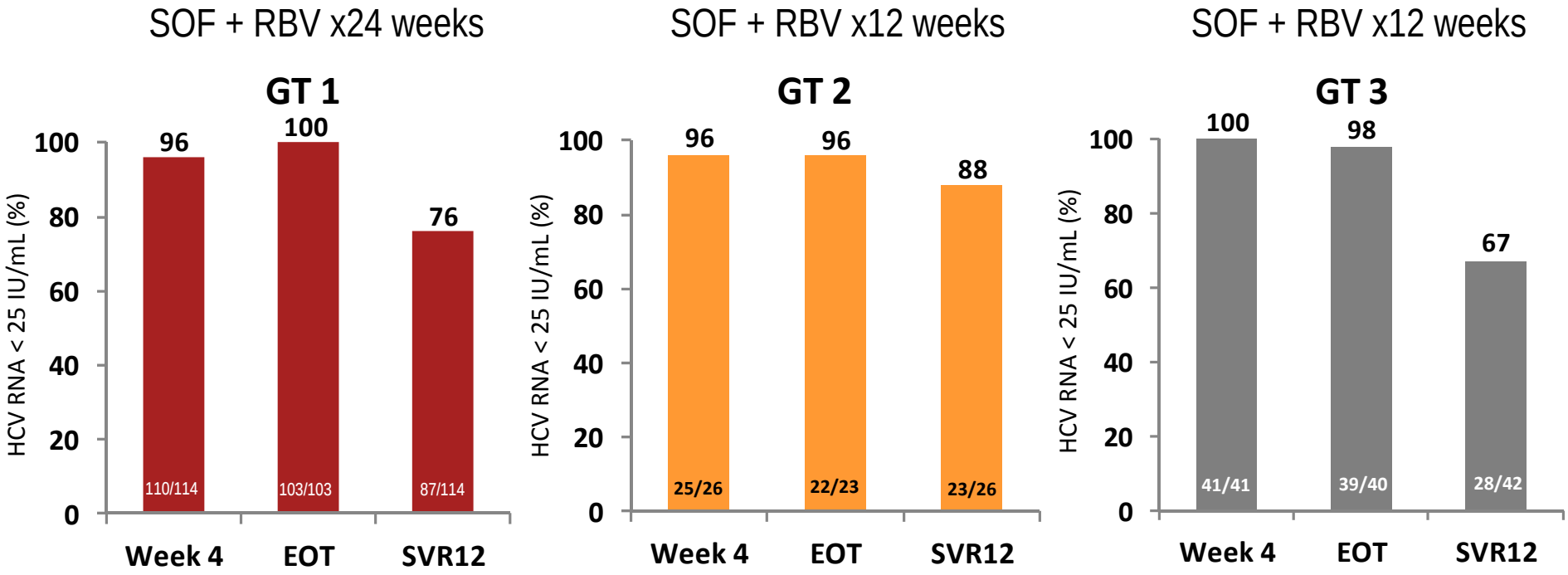
* Eleven GT3 patients that completed 12 weeks of SOF + RBV were included in safety analysis

Extending treatment duration to 24 weeks did not increase the incidence of laboratory abnormalities

Zeuzem S, et al. AASLD 2013. Washington, DC. #1085

All-Oral Therapy of SOF + RBV in Treatment-Naive HIV/HCV Coinfection

PHOTON-1 Virologic Response

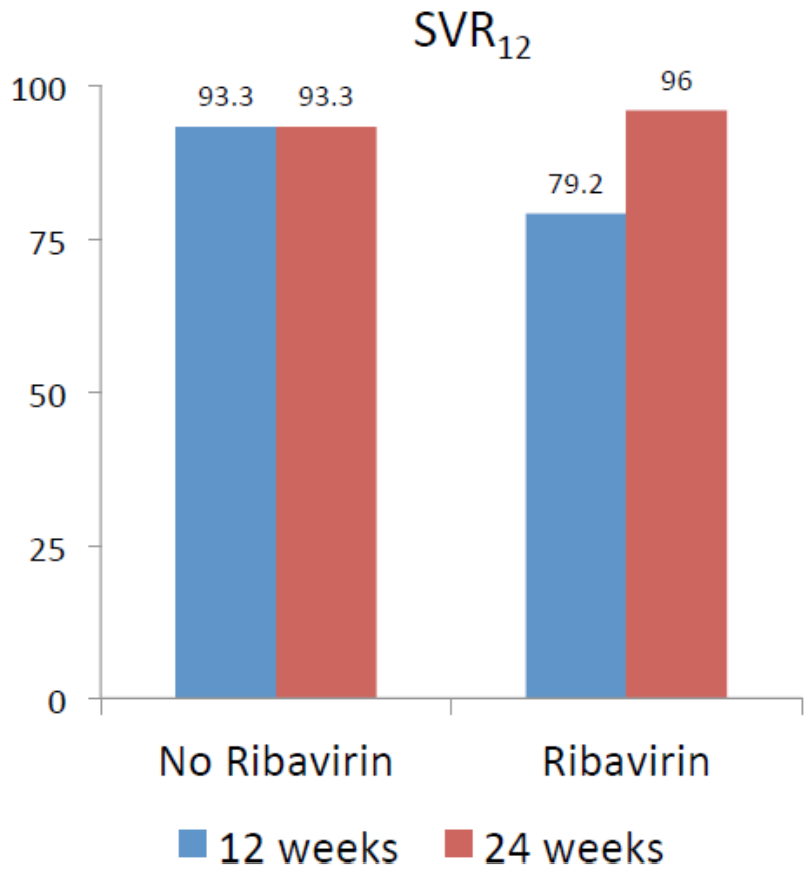


- An all-oral regimen of SOF + RBV for 12–24 weeks resulted in high SVR12 rates in TN HIV-infected patients with GT 1, 2 and 3 coinfection – with SVR12 rates similar to mono-infection
- No HCV resistance (S282T) was observed in virologic failures via deep sequencing
- Two patients had HCV breakthrough; both had documented non-adherence to SOF
- Two patients had transient HIV breakthrough; both had documented non-adherence to ART

Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212

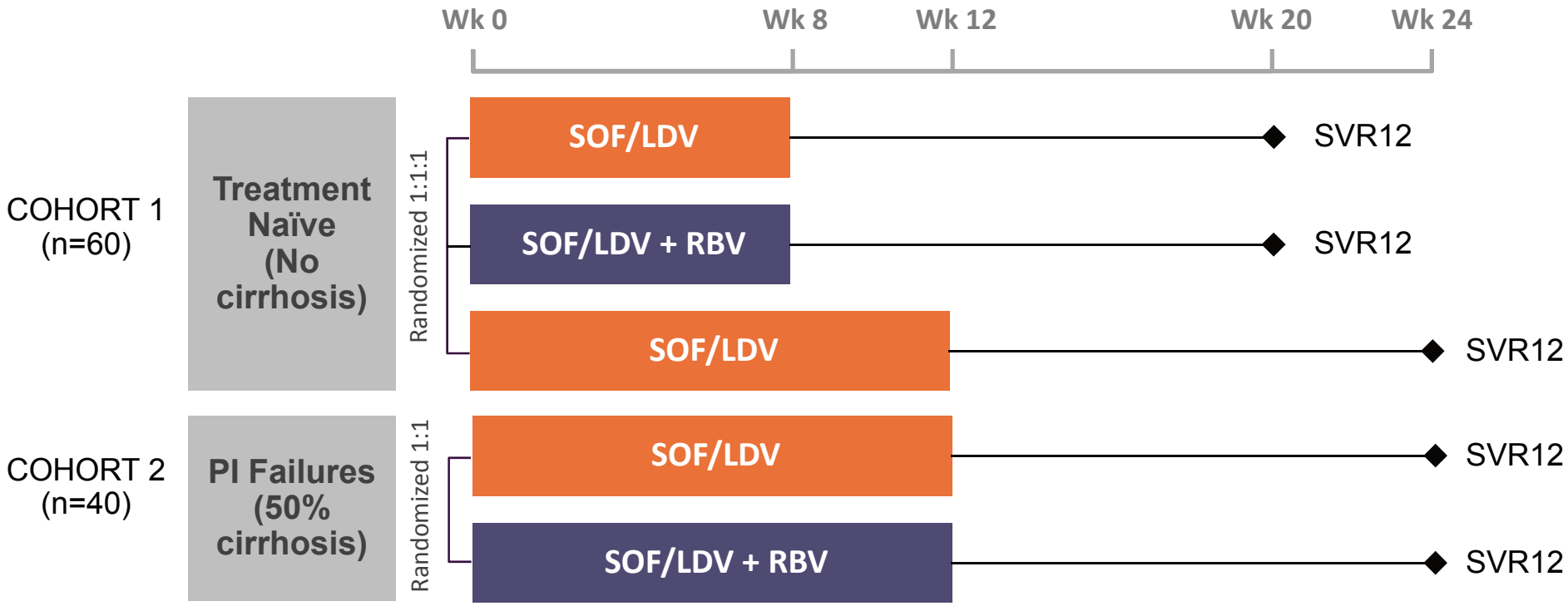
Simeprevir + sofosbuvir with or without RBV in genotype 1 treatment-naïve and prior null responder patients: COSMOS

- Cohort 1 (n=80): Null responders with METAVIR F0-2
  - Black, 28.8%
  - Genotype 1a, 77%; Q80K 50%
  - IL28B CC, 6%
  - F2, 59%
- SVR_{12} for 1a/Q80K: 24 of27 (89%) excluding non-virologic failures
- Non-SVR patients (n=8)
  - No breakthrough
  - Viral relapse, n=3; all 1a/Q80K
  - Stop early, n= 4
  - 1 patient achieved SVR_4 followed by fatal CVA



Jacobson IM et al. The Liver Meeting 2013; LB-3

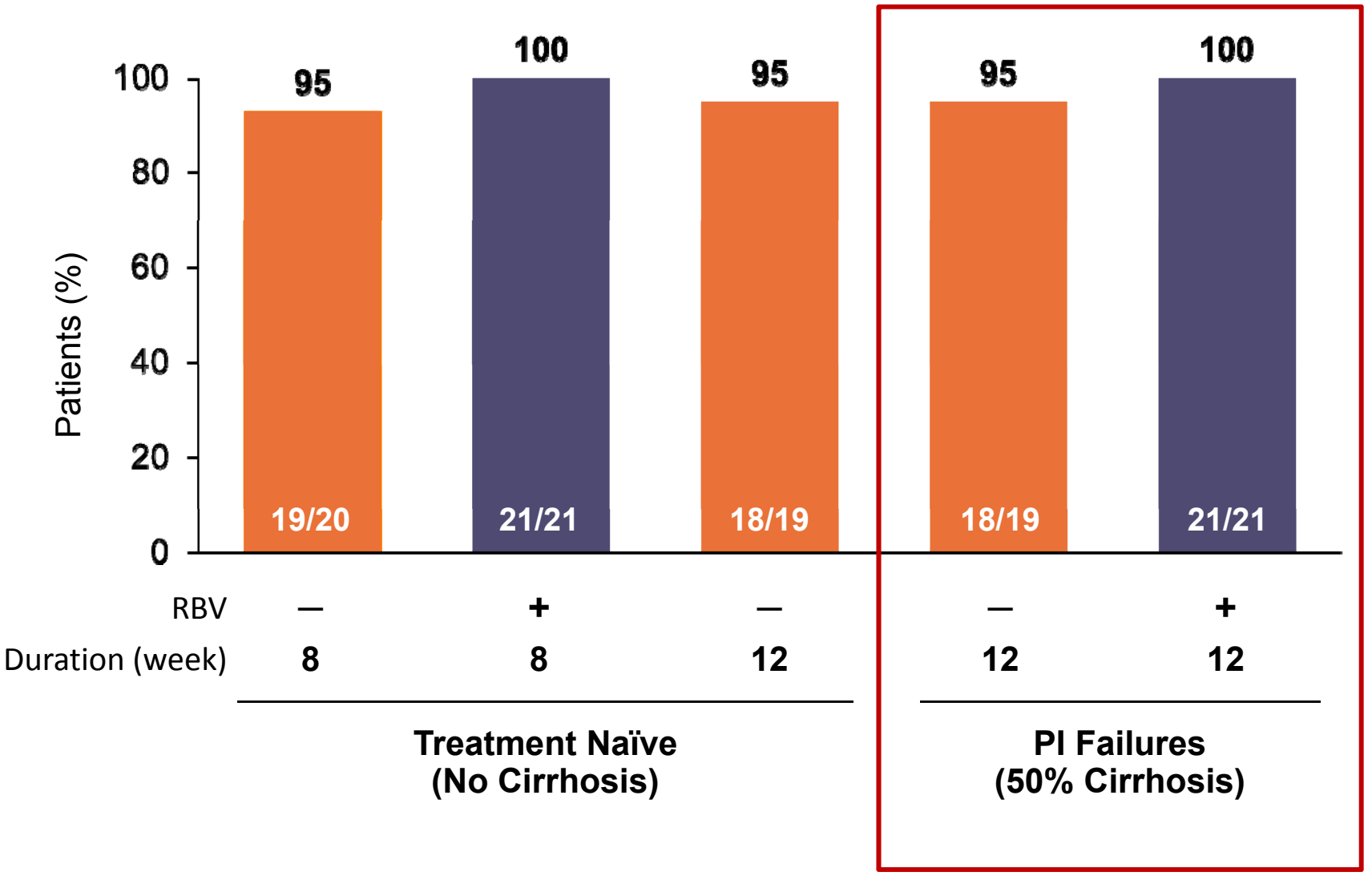
Sofosbuvir and Ledipasvir Fixed-Dose Combination with and without Ribavirin in Treatment-Naïve and Previously Treated Patients with Genotype 1 Hepatitis C:The LONESTAR Study



- Single center study of GT 1 patients
- Broad inclusion criteria
  - No upper limit to age or BMI
  - Platelets ≥50,000/mm^3

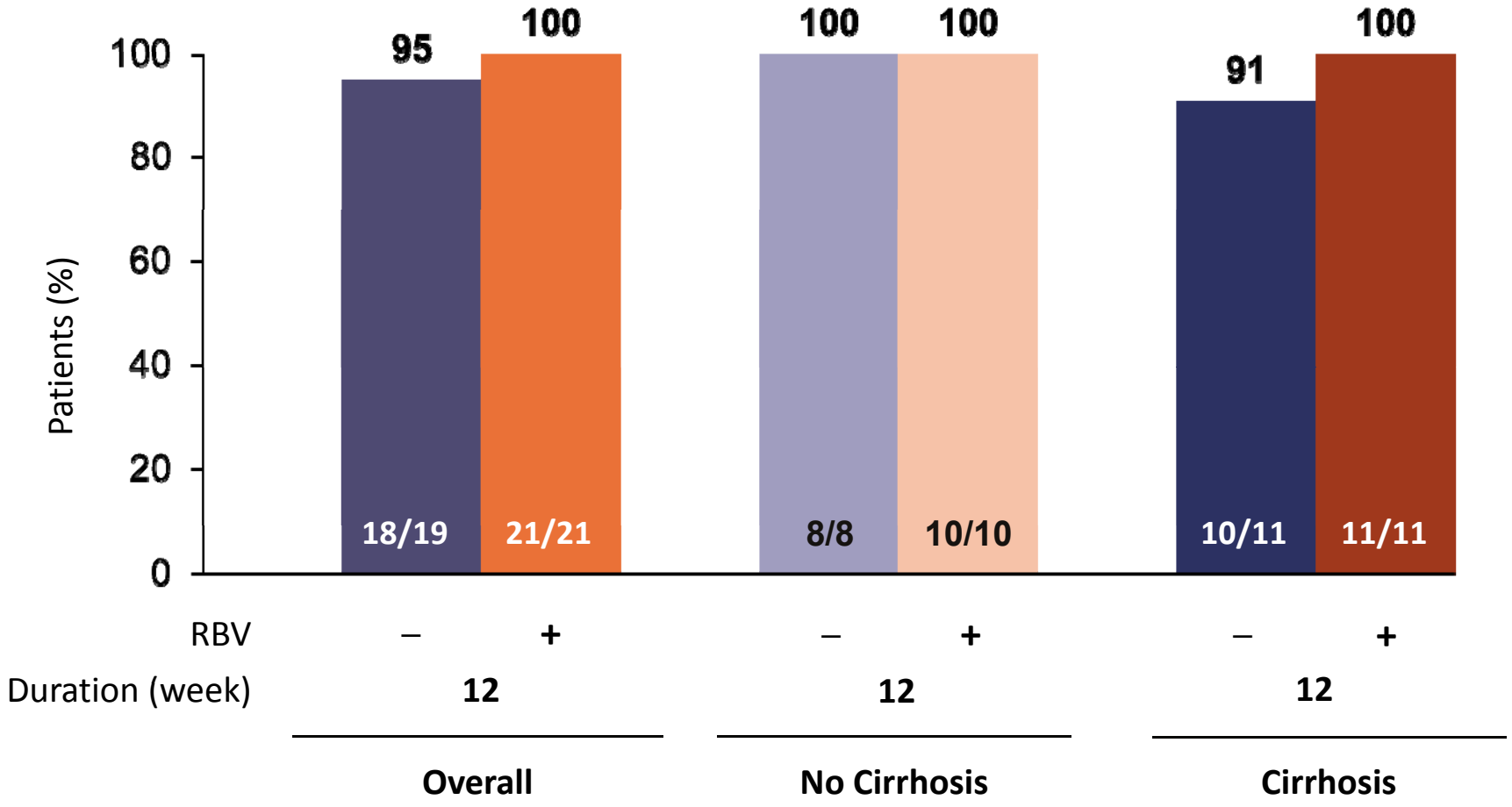
Lawitz E, et al AASLD 2013

SVR12 Results



Lawitz E, et al AASLD 2013

Patients Who Previously Failed Protease Inhibitor Therapy: With and Without Cirrhosis



Lawitz E, et al AASLD 2013

Situación actual

- Informe de Posicionamiento Terapeutico
  - Informe Cientifico
  - Revisión por Comunidades Autónomas
  - Sociedades Cientificas y Asociaciones de Pacientes

Filosofia General

- Se trata de un tratamiento revolucionario
- Mejor en eficacia y seguridad en todos los grupos de pacientes
- Puede conseguir la erradicación de la enfermedad
- Se necesita una estrategia Nacional en Hepatitis C

APRIL 2014

EASL Recommendations on Treatment of Hepatitis C 2014

Genotipo 1

Recommendation

- Patients infected with HCV genotype 1 can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(Recommendation A1)**

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks **(Recommendation B1)**
- Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **(Recommendation B1)**

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients, including those who failed on a triple combination of pegylated IFN-α, ribavirin and either telaprevir or boceprevir (pending data with 12 weeks of therapy in treatment-experienced patients) **(Recommendation B1)**
- Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis **(Recommendation B1)**