13th Course in update on HIV and Viral Hepatitis

February 1st and 2nd, 2019 (Vigo)

Management of the cured hepatitis C

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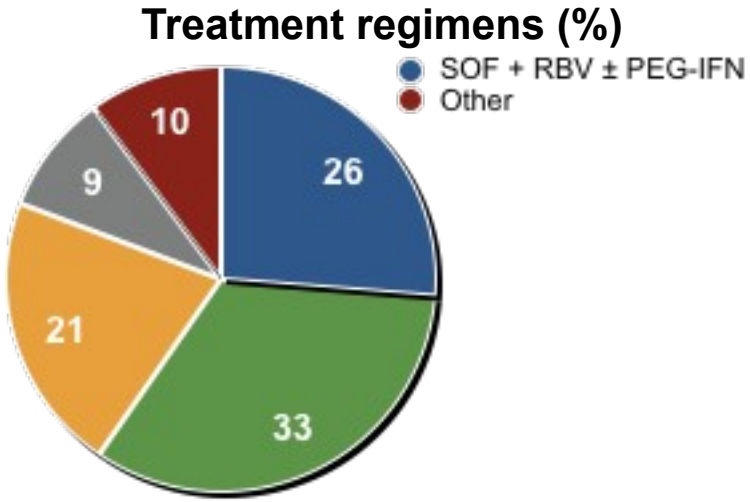
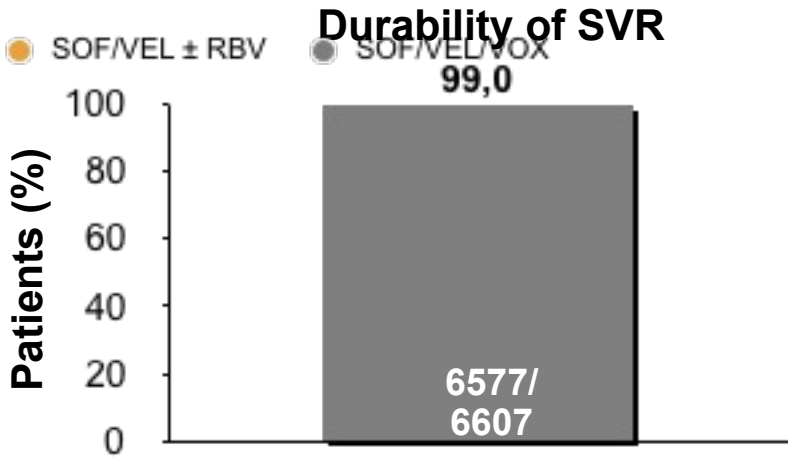
Antiviral treatment goals

- The main objective of Tx is viral eradication or sustained virological response (SVR), i.e. undetectable HCV RNA 12 weeks after the end of treatment
- SVR is associated with several clinical benefits including -QOL improvement -lost of infectivity -fibrosis reversal -reduction in the risk of decompensation and HCC -reduction in the risk of liver related mortality and overall mortality

Long-term follow-up study of patients who achieved SVR in Gilead-sponsored trials (Gilead SVR Registry)

- 3-year registry of patients (N=6607) treated in Gilead-sponsored trials who achieved SVR





- 30 patients had detectable HCV RNA during their participation in the SVR registry
- 8 (0.1%) had virological evidence of relapse
- 15 (0.2%) had virological evidence of reinfection with phylogenetically distinct virus of same genotype
- 7 (0.1%) had reinfection with different genotype

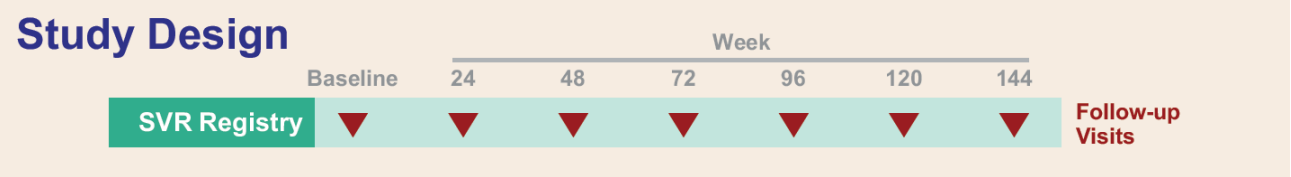
SVR is durable and late relapses (beyond post-treatment Week 12) are rare

Schwabe C, et al. AASLD 2018; Poster #595

LDV: ledipasvir; PEG-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virological response; VEL: velpatasvir; VOX: voxilaprevir

Gilead SVR registry: long-term outcomes from >6600 patients treated with SOF-based regimens

- 3-year registry study of patients treated in Gilead-sponsored trials who achieved SVR§

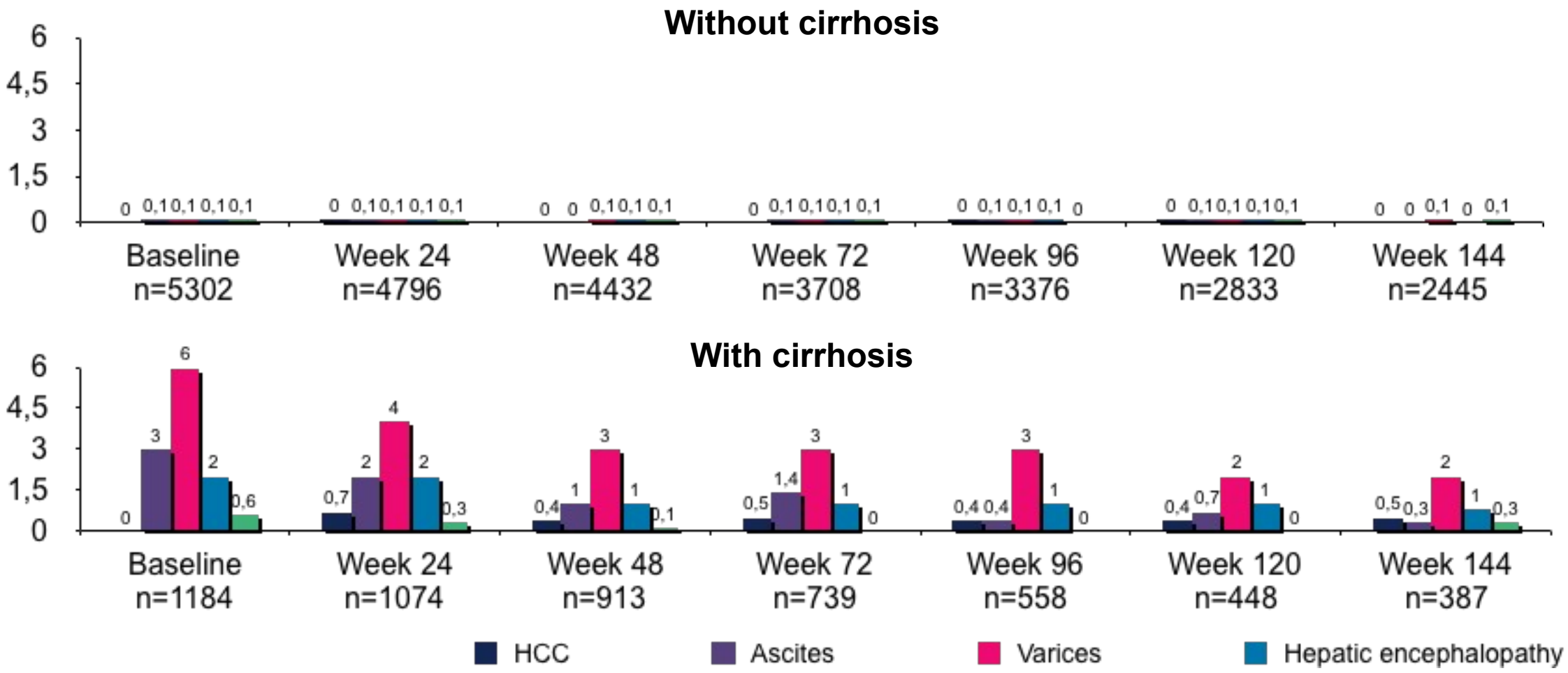


	SOF+ RBV ± PEG-IFN (n=1724)	LDV/SOF ± RBV (n=2204)	SOF/VEL ± RBV (n=1422)	SOF/VEL/VOX (n=597)	Other (n=660)	Total (N=6607)
Mean age, y (range)	52 (19–76)	55 (19–83)	55 (20–82)	56 (23–82)	51 (20–76)	54 (19–83)
Male, n (%)	1117 (65)	1404 (64)	844 (60)	364 (61)	373 (57)	4102 (62)
Race/ethnicity* White Hispanic/Latino	 1489 (86) 203 (12)	 1843 (84) 217 (10)	 1194 (84) 128 (9)	 486 (81) 52 (9)	 562 (85) 69 (10)	 5574 (84) 669 (10)
Cirrhosis, n (%)	349 (20)	526 (24)	200 (14)	51 (9)	61 (9)	1187 (18)**
IL28B CC, n (%)	613 (36)	500 (23)	431 (30)	157 (26)	259 (39)	1960 (30)
HCV genotype, n (%) 1 / 2 / 3 / 4 / 5 / 6 / other†	 (44) / 70 (4) / 1 (<1) / 3 (<1) / 0	 (1) / 23 (1) / 3 (<1) / 5 (<1)	 (27) / 109 (8) / 27 (2) / 37 (3) / 0	 340 (57) / 64 (11) / 108 (18) / 49 (8) / 14 (2) / 19 (3) / 3 (<1)	 651 (99) / 3 (<1) / 6 (<1) / 0 / 0 / 0 / 0	 4233 (64) / 695 (11) / 1289 (20) / 255 (4) / 65 (1) / 62 (<1) / 8 (<1)

Schwabe C, et al. AASLD 2018; Poster #595

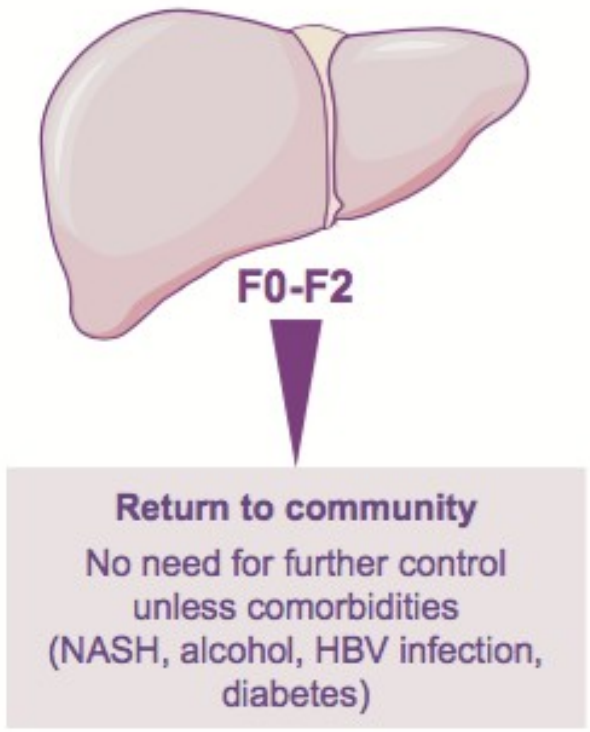
§Sustained virological response at last visit. *Based on data collected from treatment studies; **Among patients with cirrhosis, mean CTP score at baseline was 5.2 (range 5–10); †Mixed/indeterminate/missing.
CTP: Child–Turcotte–Pugh; LDV: ledipasvir; PEG-IFN: interferon; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

Clinical events were infrequent, but more often reported in patients with baseline cirrhosis



Schwabe C, et al. AASLD 2018; Poster #595

We can discharge patients with F0-F2 with the only caution of co-morbidities



against and does not indicate active infection or protect a possible new infection

No reasons to repeat HCV RNA testing

Periodic retesting should be considered for those with ongoing risk of acquisition or reinfection

Long-Term Follow-up of Patients with Chronic HCV Infection and Compensated or Decompensated Cirrhosis Following Treatment with Sofosbuvir-Based Regimens

Alessandra Mangia[1], Eric Lawitz[2], Edward Gane[3], Brian Conway[4], Peter J. Ruane[5], Armando Abergel[6], Brian McNabb[7], Anu Osinusi[7], Frances Chen[7], Hadas Dvory-Sobol[7], Diana M. Brainard[7], G. Mani Subramanian[7], Barbara Leggett[8], Jose Luis Calleja[9], Kosh Agarwal[10], Ziad Younes[11], Andrew Muir[12]

[1]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; [2]Texas Liver Institute, University of Texas Health San Antonio, TX, USA; [3]New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; [4]Vancouver Infectious Diseases Centre, Vancouver, BC, Canada; [5]Ruane Medical & Liver Health Institute, Los Angeles, CA, USA; [6]Centre Hospitalier Universitaire Estaing Clermont-Ferrand, France; [7]Gilead Sciences Inc., Foster City, CA, USA; [8]School of Medicine, University of Queensland, Brisbane, Australia; [9]Hospital Universitario Puerta de Hierro, Madrid, Spain; [10]Kings College Hospital NHS Trust Foundation, London, UK; [11]GastroOne, Germantown, TN, USA; [12]Duke University School of Medicine, Durham, NC, USA

EASL 2018, Paris

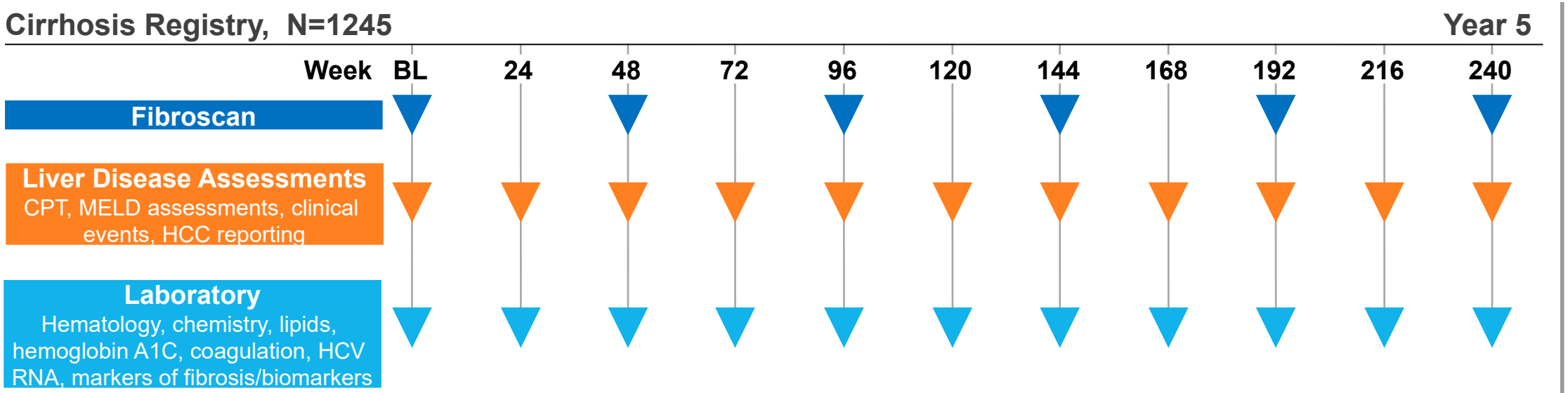
Results: Demographics and Baseline characteristics

		CPT A n=1039	CPT B+C n=206
Mean age, y (range)		59 (26–86)	60 (40–77)
Male, n (%)		726 (70)	144 (70)
White, n (%)		919 (89)	181 (88)
Mean body mass index, kg/m^2 (range)		29 (18–57)	29 (18–46)
HCV genotype, n (%)	1	599 (58)	179 (87)
	2	61 (6)	9 (4)
	3	315 (30)	13 (6)
	4	53 (5)	4 (2)
	5	9 (<1)	0
	6	2 (<1)	1 (<1)
Treatment experienced, n (%)		687 (66)	130 (63)
Parent study HCV regimen	SOF + RBV	62 (6)	10 (5)
	LDV/SOF ± RBV	268 (26)	70 (34)
	SOF/VEL ± RBV	305 (29)	126 (61)
	SOF/VEL/VOX	307 (30)	0
	SOF + other	97 (9)	0
Median time from SVR to registry start, wk (range)		*30 (5–181)*	*44 (11–119)*

All except age were assessed pretreatment (baseline of the parent study). LDV, ledipasvir; RBV, ribavirin; VEL, velpatasvir; VOX, voxilaprevir.

Mangia et al EASL 2018

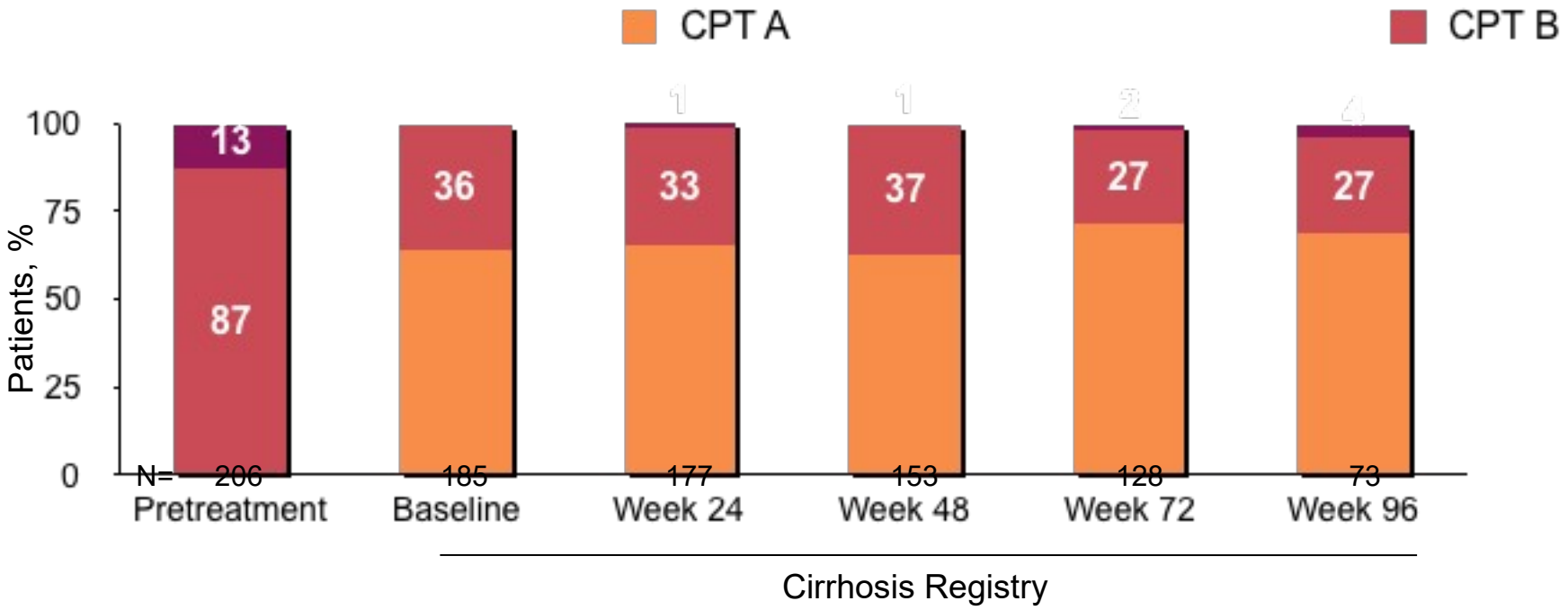
Key Eligibility Criteria / Study Design



Other assessments included quality of life surveys, DNA, endoscopy and optional biopsy.
CPT, Child-Pugh Turcotte; MELD, model for end-stage liver disease.

- Eligible patients had
  - –SVR from an IFN-free, SOF-based regimen from a Gilead-sponsored parent study
  - –Cirrhosis prior to treatment in the parent study as defined by the parent study protocol
- For patients with virologic failure, relapse was distinguished from reinfection by phylogenetic analyses of samples collected pretreatment and posttreatment at time of failure

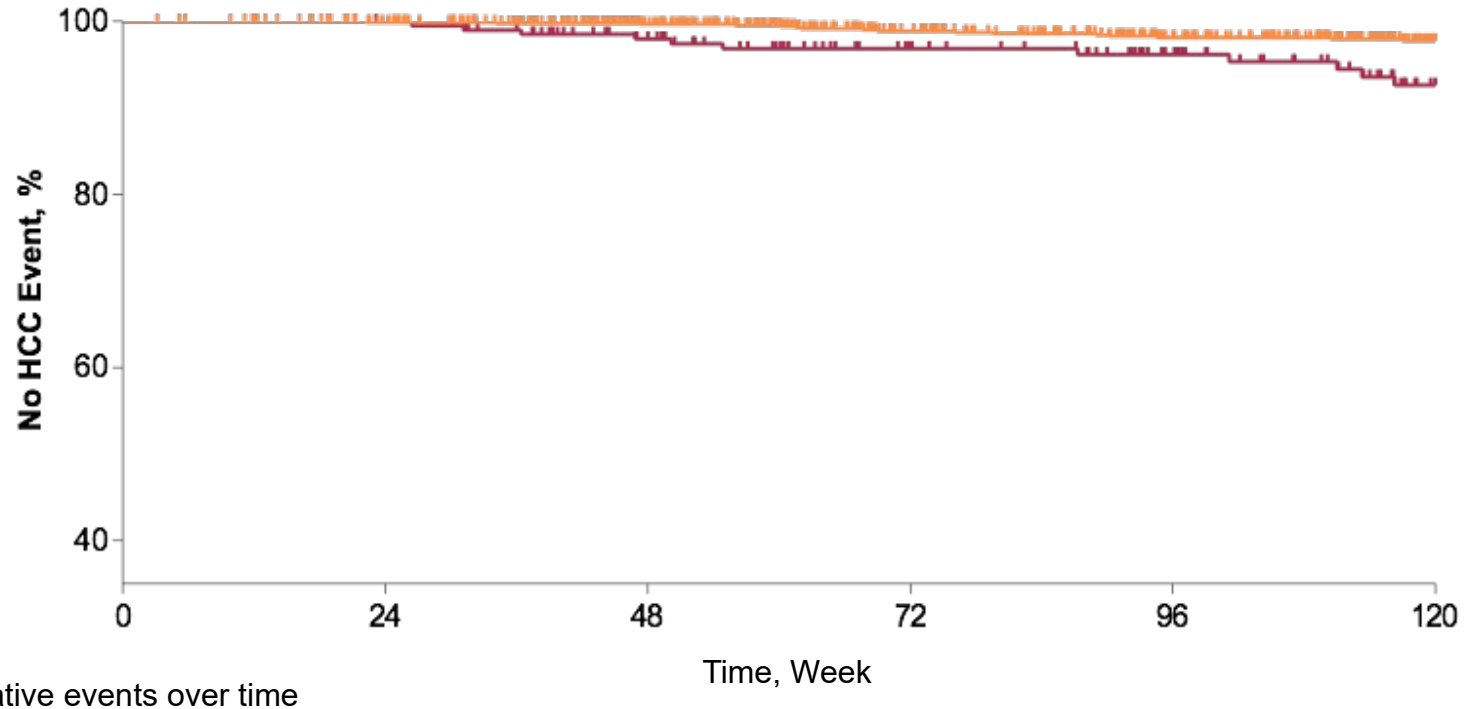
Results: CPT Class Shifts in Patients with CPT B+C Cirrhosis



- Among patients with CPT A cirrhosis at pretreatment, at Week 96, 99% remained at CPT A

Mangia et al EASL 2018

Results: KM Plot of Time to HCC Since Achieving SVR12



Incidence Rate	CPT A n=1039	CPT B+C n=206
P-Ys Follow up	2216	439
Number of Events	23	23
Exposure adjusted incidence rate/100 PYs	**1.04**	**5.23**

Cumulative events over time
(at risk /events)

CPT A	1037 (0)	1014 (2)	868 (7)	677 (7)	592 (12)	466 (16)
CPT B+C	205 (0)	200 (4)	185 (11)	174 (16)	151 (19)	90 (20)

Mangia et al EASL 2018

Incidence and Predictors of de Novo Hepatocellular Carcinoma Following Achievement of Sustained Virologic Response With Direct-Acting Antivirals: Results From the Gilead SVR and Cirrhosis Registries

K. Rajender Reddy,[1] Ira M. Jacobson,[2] Armand Abergel,[3] Barbara Leggett,[4] Charles Landis,[5] Robert H. Hyland,[6] Frances Chen,[6] Liyun Ni,[6] Anu Osinusi,[6] Diana M. Brainard,[6] Jose Luis Calleja Panero,[7] Eric Lawitz,[8] Andrew Muir,[9] Alessandra Mangia[10]

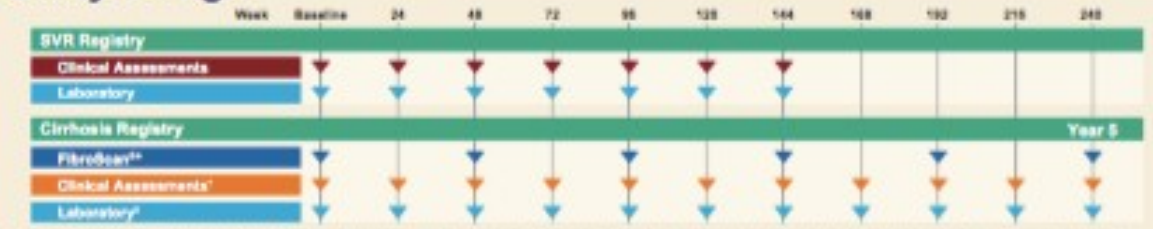
[1]University of Pennsylvania, Philadelphia; [2]NYU School of Medicine, New York, NY; [3]Centre Hospitalier Universitaire Estaing de Clermont-Ferrand, France; [4]Faculty of Medicine, The University of Queensland, Brisbane, Australia; [5]UW Medical Center, Seattle, WA; [6]Gilead Sciences Inc., Foster City, CA; [7]Hospital Universitario Puerta de Hierro–Majadahonda, Spain; [8]UT Health San Antonio, TX; [9]Duke University School of Medicine, Durham, NC; [10]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy

Demographics and Baseline Characteristics

		No Cirrhosis n=4592	Compensated Cirrhosis n=1913	Decompensated Cirrhosis n=292	Unknown n=11	Overall N=6808
Demographics and Baseline Characteristics	Mean age, y (range)	54 (19–82)	58 (23–87)	60 (29–76)	61 (51–71)	55 (19–87)
	Male, n (%)	2767 (60)	1310 (68)	206 (71)	8 (73)	4291 (63)
	White, n (%)	3840 (84)	1651 (86)	266 (91)	9 (82)	5766 (85)
	Mean BMI, kg/m² (range)	27 (17–66)	29 (18–172)	29 (18–58)	29 (19–44)	28 (17–172)
	HCV GT, n (%)					
	1	2799 (61)	1139 (60)	260 (89)	7 (64)	4205 (62)
	2	577 (13)	142 (7)	10 (3)	2 (18)	731 (11)
	3	897 (20)	522 (27)	13 (4)	2 (18)	1434 (21)
	4	208 (5)	77 (4)	6 (2)	0	291 (4)
	5	52 (1)	14 (<1)	0	0	66 (1)
	6	52 (1)	9 (<1)	1 (<1)	0	62 (<1)
	Missing or mixed	7 (<1)	10 (<1)	2 (<1)	0	19 (<1)
	IL28B, n (%)					
	CC	1328 (29)	436 (23)	66 (23)	2 (18)	1829 (27)
	CT	2496 (54)	888 (46)	150 (51)	8 (73)	3542 (52)
	TT	761 (17)	309 (16)	54 (18)	1 (9)	1125 (17)
	HCV treatment experienced, n (%)	1560 (34)	1068 (56)	174 (60)	7 (64)	
Pretreatment Laboratory Values	Mean ALT, U/L	20	27	26	22	22
	Mean albumin, g/dL (SD)	4.2 (0.31)	4.3 (0.38)	3.7 (0.51)	4.4 (0.42)	4.2 (0.36)
	Albumin >3.5, n (%)	4503 (98)	1836 (96)	186 (64)	10 (91)	6535 (96)
	Mean platelets, x10³/µL (SD)	231 (66)	157 (68)	85 (48)	258 (84)	204 (77)
	Platelets >150 x10³/µL, n (%)	4227 (92)	918 (48)	27 (9)	10 (91)	5182 (76)
	HbA1c ≥5.7%, n (%)	1232 (27)	647 (34)	67 (23)	5 (45)	1951 (29)

ALT, alanine aminotransferase; BMI, body mass index; GT, genotype; HbA1c, hemoglobin A1c; IL28B, interleukin 28B.

Study Design



Multivariate Analysis

Variable	Comparison	Hazard Ratio (95% CI)	p-Value
Age, y	≥ vs <60	2.4 (1.5–3.7)	<0.001
CPT	A vs no cirrhosis	7.8 (3.3–18.4)	<0.001
	B vs no cirrhosis	15.9 (5.8–44.2)	<0.001
	C vs no cirrhosis	9.7 (2.2–42.9)	0.003
	B/C vs no cirrhosis	12.4 (4.0–38.3)	<0.001
Pretreatment baseline platelets, x10³/µL	≤ vs >150	1.8 (1.0–3.2)	0.04
Sex	Male vs female	1.9 (1.1–3.2)	0.02
HCV GT	3 vs other	2.3 (1.4–3.9)	0.002
HCV treatment experience	Experienced vs naïve	2.0 (1.2–3.3)	0.01
Pretreatment baseline albumin, g/dL	≤3.5 vs >3.5	2.3 (1.3–3.9)	0.004

CI, confidence interval.

Incidence and Predictors of de Novo Hepatocellular Carcinoma Following Achievement of Sustained Virologic Response With Direct-Acting Antivirals: Results From the Gilead SVR and Cirrhosis Registries

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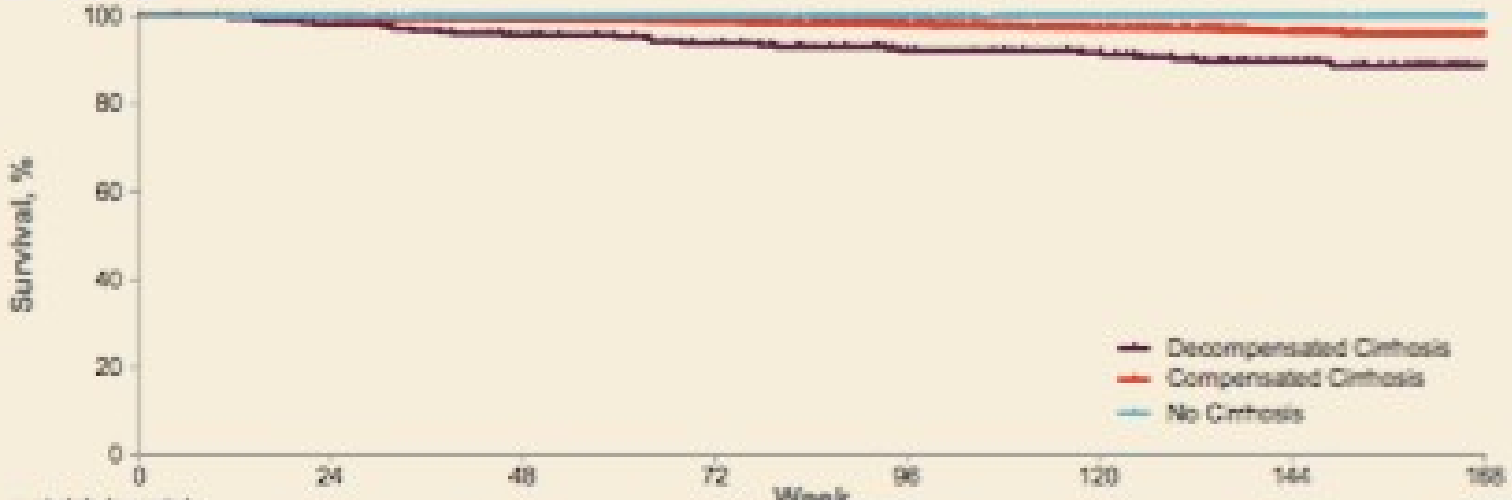
Kaplan-Meier Plot of Patients Without HCC Since Achieving SVR12



n at risk (events)							
No cirrhosis	4444 (4)	4199 (5)	3543 (5)	3206 (5)	2678 (7)	2331 (7)	686 (7)
Compensated	1859 (4)	1774 (15)	1622 (23)	1364 (35)	1135 (44)	922 (53)	541 (56)
Decompensated	281 (5)	257 (12)	238 (17)	208 (21)	196 (22)	163 (26)	79 (28)

HCC: Exposure-Adjusted Incidence Rates

	No Cirrhosis n=4592	Compensated Cirrhosis n=1913	Decompensated Cirrhosis n=292	Unknown n=11	Overall N=6803
PY of follow-up	11,013.13	4924.76	740.85	31.66	16,710.40
No. of observed events	8	64	30	0	102
Exposure-adjusted incidence rate, /100 PY	0.07	1.30	4.05	0	0.61

PY, person-years.

Post-Tx

Long-term follow-up – hepatocellular carcinoma (HCC)

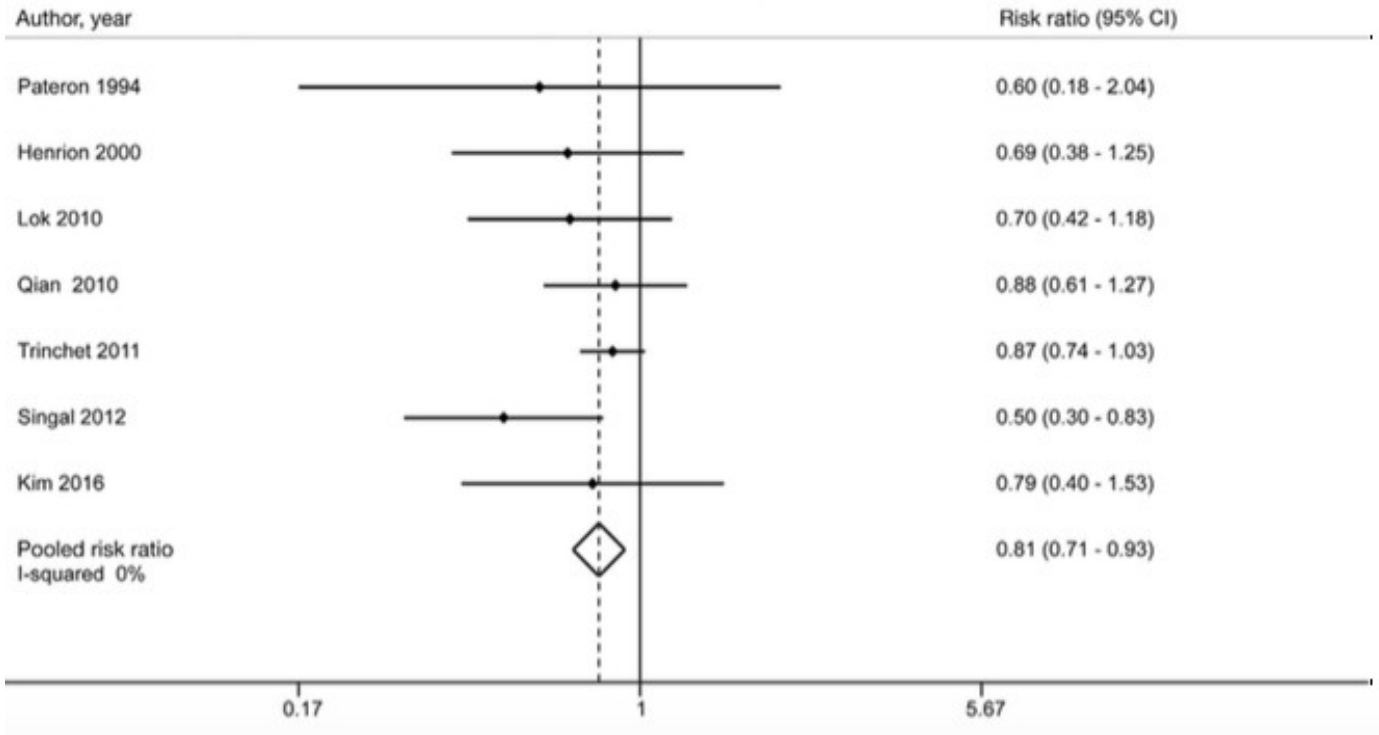
	F0–F3	F4+
World Health Organization	No specific follow-up recommendations given	Ultrasound surveillance and/or alpha-fetoprotein estimation every 6 months
EASL European Association for the Study of the Liver	Discharge provided they have no further comorbidities	Ultrasound surveillance for HCC every 6 months
AASLD American Association for the Study of Liver Diseases; IDSA Infectious Diseases Society of America	Follow-up as if they were never infected with HCV	Ultrasound surveillance for HCC every 6 months

F: fibrosis stage

WHO. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. July 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1; EASL. J Hepatol 2018;69:461–511; AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. (all websites accessed January 2019)

Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis

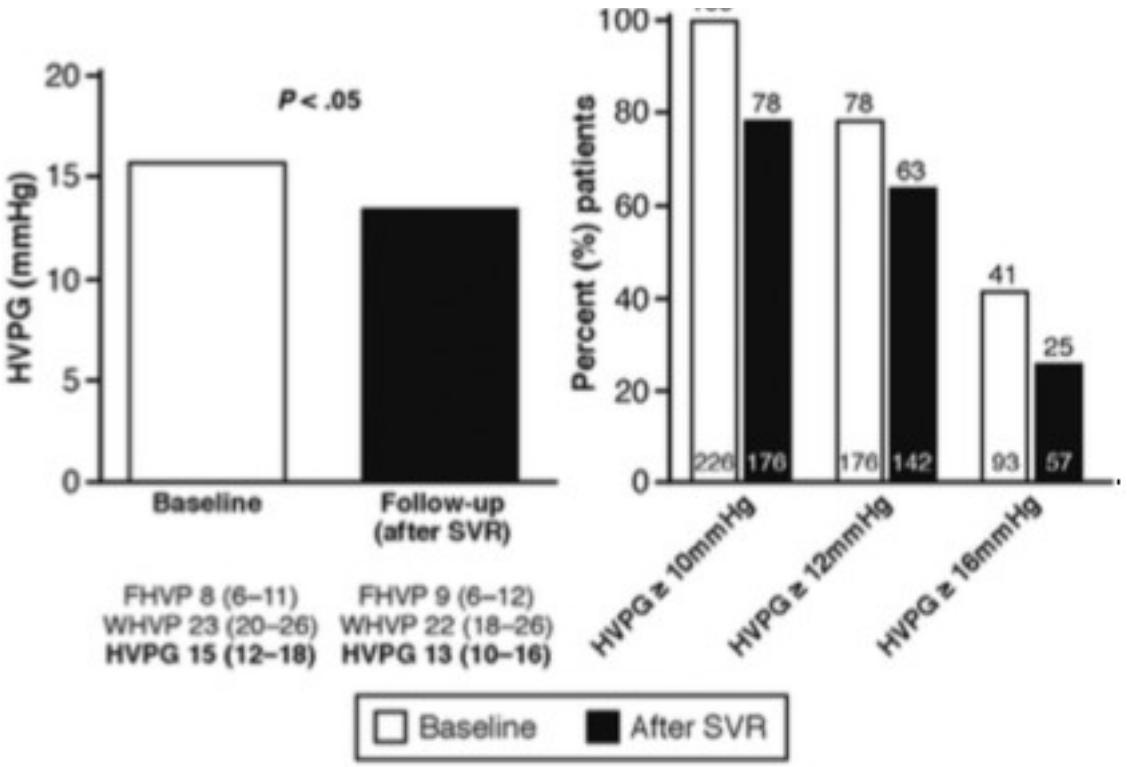
Kristina Tzartzeva,[1,*] **Joseph Obi,**[1,*] Nicole E. Rich,[1] Neehar D. Parikh,[2] Jorge A. Marrero,[1] Adam Yopp,[3] Akbar K. Waljee,[2,4] and Amit G. Singal[1,5]



Reintroduction of AFP as an adjunct to ultrasound due to better real life performance and potential to detect infiltrative disease

Effects of All-Oral Anti-Viral Therapy on HVPG and Systemic Hemodynamics in Patients With Hepatitis C Virus-Associated Cirrhosis

	Overall cohort n = 226
Sex (male) (n, %)	121 (53)
Age (*y*)	60 (53-69)
BMI, *kg/m²*	27 (24-30)
Arterial hypertension (n, %)	69 (30)
Diabetes mellitus (n, %)	61 (27)
Metformin (n, %)	38 (17)
Insulin (n, %)	27 (12)
Statins (n, %)	9 (4)
Genotype (n, %)	
1a	27 (12)
1b	159 (70)
2	4 (2)
3	17 (7.5)
4	18 (8)
5	1 (0.5)
Naive (n,%)	116 (51)
Esophageal varices[a] (n, %)	157 (75)
Small	89
Large	68
NSBB therapy (n,%)	103 (47)
Previous decompensation[b] (n, %)	66 (29)
Ascites	51 (23)
AVB	26 (11)
HE	12 (5)
Hepatocellular carcinoma (n, %)	7 (3)
ALT (*IU/L*)	69 (44–110)
Bilirubin (*mg/dL*)	1.1 (0.8–1.5)
Albumin (*g/dL*)	3.9 (3.4–4.2)
Albumin ≤3.5 (n, %)	68 (30)
Platelet count/10^9	84 (61–115)
Platelet count ≤90 (n, %)	126 (56)
INR	1.17 (1.08–1.27)
Child-Pugh Turcotte (n, %)	
CPT A	179 (79)
CPT B	47 (21)
MELD score	9 (7–11)
Liver stiffness (LSM) kPa[c]	27 (20–37)



HVPG: hepatic venous pressure gradient; FHVP: free hepatic venous pressure; WHVP: wedged hepatic venous pressure

Lens S et al Gastroenterology 2016

Long-term follow-up – varices

Post-Tx

	F0–F3	F4+
World Health Organization	No specific follow-up recommendations given	Endoscopy every 1–2 years to exclude oesophageal varices
EASL European Association for the Study of the Liver	Discharge provided they have no further comorbidities	Surveillance by endoscopy should be performed if varices were present at pre-treatment endoscopy
AASLD American Association for the Study of Liver Diseases; IDSA Infectious Diseases Society of America	Follow-up as if they were never infected with HCV	Patients in whom varices are found pre-treatment should be followed as indicated

WHO. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. July 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1; EASL. J Hepatol 2018;69:461–511; AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. (all websites accessed January 2019)

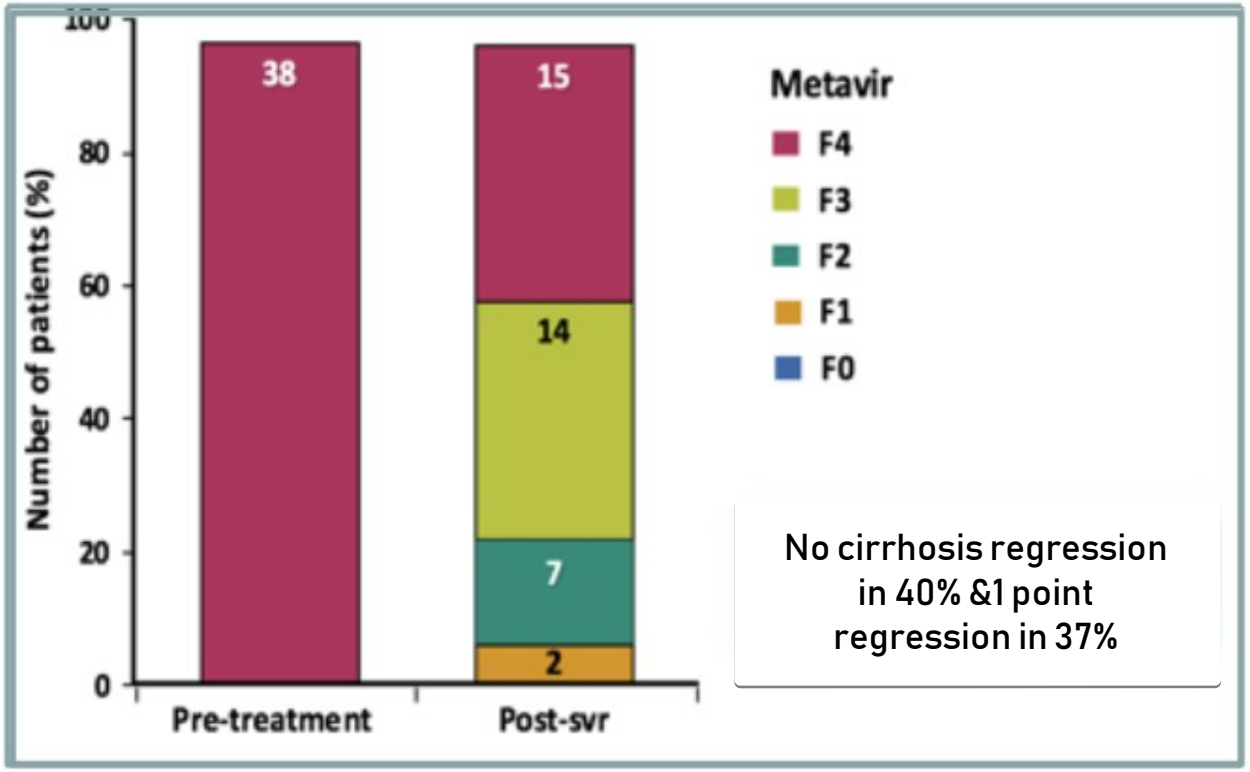
Baveno VI Consensus Workshop report

In patients with virus related cACLD non-invasive methods are sufficient to rule-in CSPH, defining the group of patients at risk of having endoscopic signs of PH: Liver stiffness by TE (20–25 kPa; at least two measurements on different days in fasting condition; caution should be paid to flares of ALT.

Surveillance of oesophageal varices (changed from Baveno V). In compensated patients with no varices at screening endoscopy and with ongoing liver injury (e.g. active drinking in alcoholics, lack of SVR in HCV), surveillance endoscopy should be repeated at 2 year intervals (5;D).
In compensated patients with small varices and with ongoing liver injury (e.g. active drinking in alcoholics,lack of SVR in HCV), surveillance endoscopy should be repeated at one year intervals (5;D).
In compensated patients with no varices at screening endoscopy in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors(e.g. obesity), surveillance endoscopy should be repeated at three year intervals (5;D).
In compensated patients with small varices at screening endoscopy in whom the aetiological factor has been removed (e.g. achievement of SVR in HCV; long-lasting abstinence in alcoholics) and who have no co-factors(e.g. obesity), surveillance endoscopy should be repeated at two year intervals (5;D).

Journal of Hepatology 2015 vol. 63 | 743–752

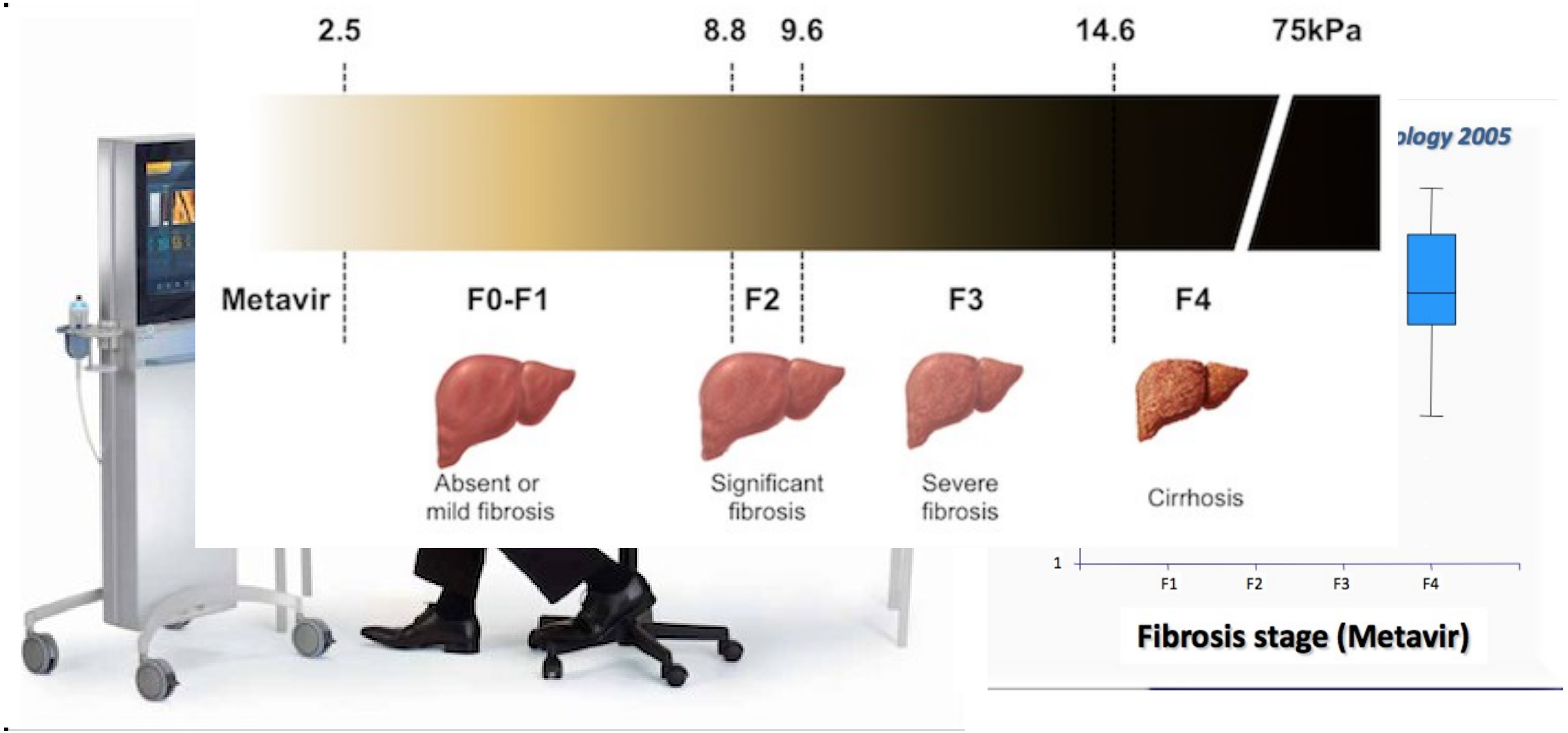
Second biopsy in 38 patients 5 yrs after SVR to Peg IFN-RBV : 6-monthly surveillance*



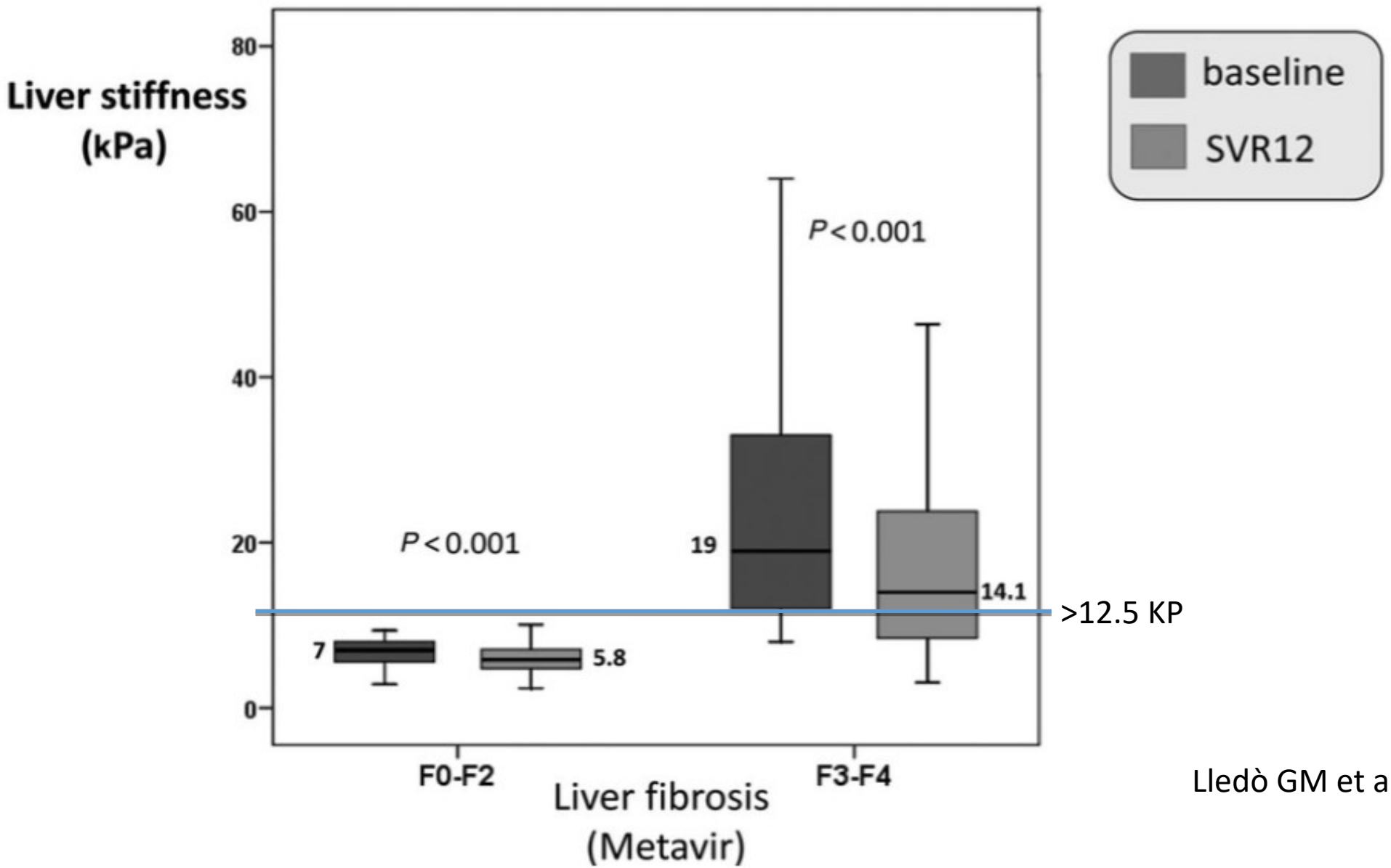
No cirrhosis regression in 40% &1 point regression in 37%

*D'Ambrosio et al Hepatology 2012;

How can we alternatively “measure” fibrosis?



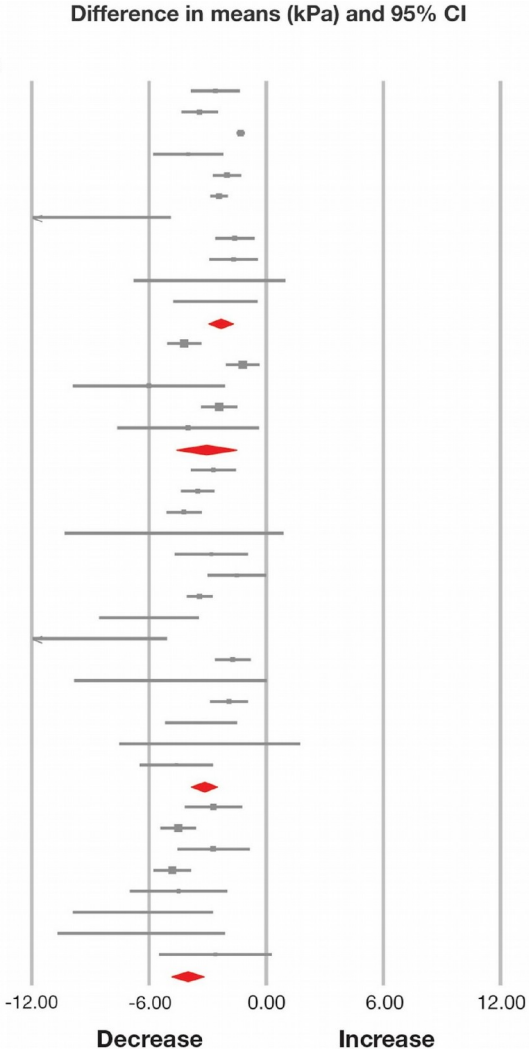
Does liver fibrosis improve after DAA treatment?



Lledò GM et al AIDS 2018

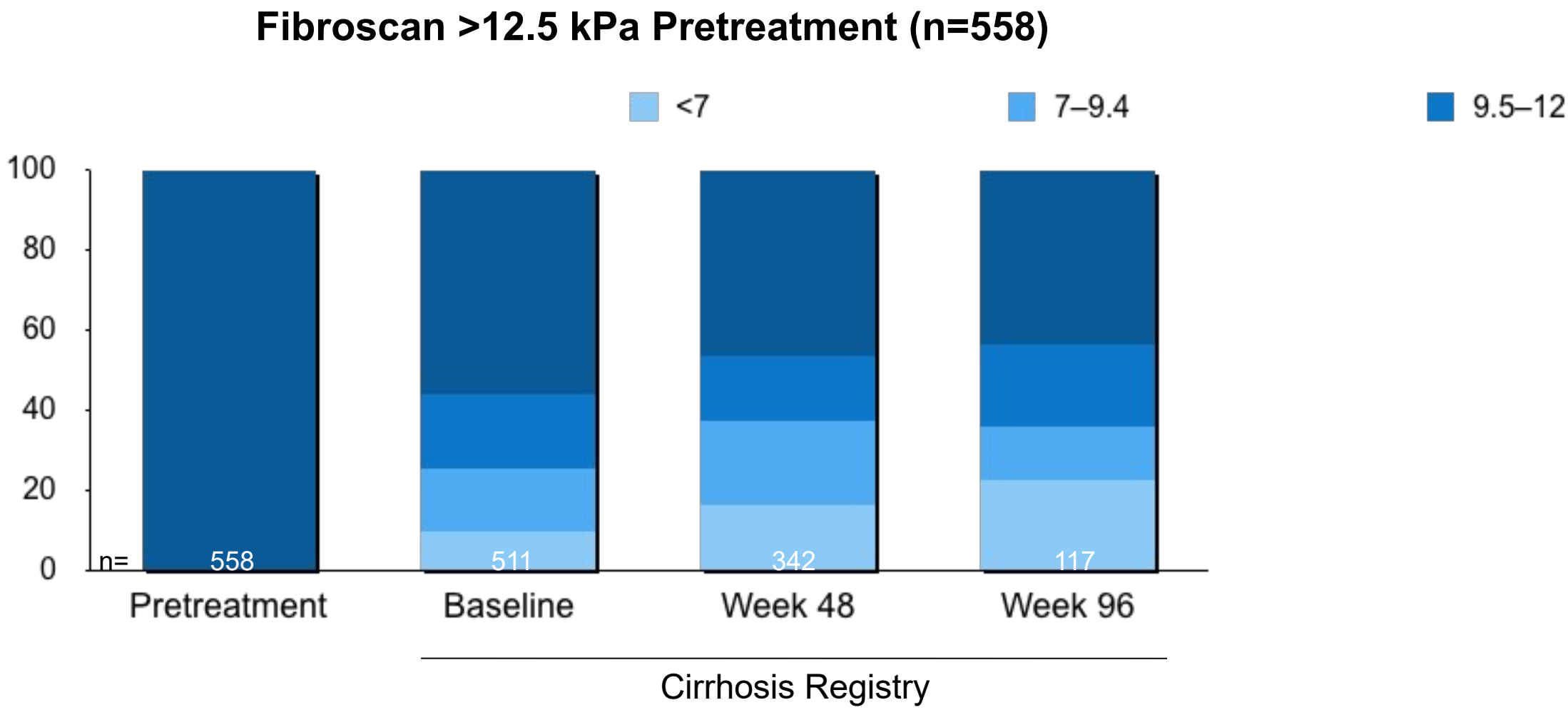
Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis

Study name	Time point	Difference in means (kPa)	Lower limit	Upper limit	*P*-value
Arima 2010		-2.60	-3.90	-1.30	.00
Carton 2013		-3.40	-4.37	-2.43	.00
El Saadany 2016 - F0/1		-1.30	-1.55	-1.05	.00
El Saadany 2016 - F2/3		-4.00	-5.83	-2.17	.00
Hezode 2011		-2.00	-2.77	-1.23	.00
Jacob 2016		-2.40	-2.88	-1.92	.00
Knop 2016		-11.10	-17.36	-4.84	.00
Martinez 2012		-1.60	-2.64	-0.56	.00
Ogawa 2009		-1.67	-2.94	-0.40	.01
Martini 2017		-2.90	-6.82	1.02	.15
Stasi 2013		-2.60	-4.79	-0.41	.02
	End of therapy (EOT)	**-2.37**	**-3.00**	**-1.74**	**.00**
Bachofner 2017		-4.20	-5.10	-3.30	.00
Bernuth 2016		-1.20	-2.09	-0.31	.01
Gamal 2015		-6.00	-9.92	-2.08	.00
Hezode 2011		-2.40	-3.37	-1.43	.00
Stradella 2016		-4.00	-7.67	-0.33	.03
	1-6m after EOT	**-3.10**	**-4.65**	**-1.55**	**.00**
Arima 2010		-2.70	-3.89	-1.51	.00
Bachofner 2017		-3.50	-4.38	-2.62	.00
Bourliere 2016		-4.20	-5.14	-3.26	.00
Bruno 2016		-4.70	-10.33	0.93	.10
Chekuri 2016		-2.80	-4.72	-0.88	.00
Crisan 2012		-1.50	-3.04	0.04	.06
Hezode 2011		-3.40	-4.09	-2.71	.00
Lens 2016		-6.00	-8.60	-3.40	.00
Knop 2016		-11.20	-17.37	-5.03	.00
Macias 2010		-1.70	-2.66	-0.74	.00
Mandorfer 2016 - HIV		-4.90	-9.87	0.07	.05
Martinez 2012		-1.90	-2.91	-0.89	.00
Ogawa 2009		-3.32	-5.19	-1.45	.00
Martini 2017		-2.90	-7.56	1.76	.22
Saez-Royuela 2016		-4.60	-6.51	-2.69	.00
	6-12m after EOT	**-3.21**	**-3.88**	**-2.55**	**.00**
Arima 2010		-2.70	-4.21	-1.19	.00
Carton 2013		-4.50	-5.45	-3.55	.00
Chekuri 2016		-2.70	-4.59	-0.81	.01
Van de Putte 2012		-4.80	-5.80	-3.80	.00
Ogawa 2009		-4.48	-7.01	-1.95	.00
Quing 2015		-6.30	-9.93	-2.67	.00
Martini 2017		-6.40	-10.72	-2.08	.00
Stasi 2013		-2.60	-5.51	0.31	.08
	>12m after EOT	**-4.07**	**-4.89**	**-3.25**	**.00**



Siddharth Singh, et al Clin Gastroenterol Hepatol 2018

Results: Fibroscan Class Shifts in Patients with Pretreatment Fibroscan >12.5 kPa



Mangia et al EASL 2018

Virologic, Clinical, and Immune Response Outcomes of Patients With Hepatitis C Virus–Associated Cryoglobulinemia Treated With Direct-Acting Antivirals

Parameters	Cryoglobulinemic vasculitis (n = 35)			Asymptomatic patients (n = 29)		
	Pretreatment	Follow-up period	*P*	Pretreatment	Follow-up period	*P*
SVR rate, n (%)	-	33 (94)	-		27 (93)	-
Cryocrit (%)	3.2 (1.5–5.7)	0.5 (0–1.4)	.01	2.6 (1.2–3)	0 (0–1.1)	.01
Circulating cryoglobulins, n (%)	35 (100)	19 (55)	-	29 (100)	11 (38)	-
C4 complement fraction, *g/L*	0.02 (0.01–0.11)	0.12 (0.05–0.16)	.01	0.09 (0.06–0.18)	0.12 (0.08-0.17)	.02
Red						
CH5						
Red						
Rhe						
Positive rheumatoid factor, n (%)	24 (65)	17 (45)	-	9 (31)	6 (20)	-
ALT level, *IU/mL*	64 (34–115)	24 (17–28)	.01	79 (51–166)	20 (16–27)	.01
Platelets, $\times 10^9$/L	123 (81–172)	159 (107–229)	.19	119 (75–155)	118 (67–170)	.98
MELD score	7 (6–9)	6 (6–8.5)	.24	9 (6–10)	8 (6–10)	.25
Creatinine level, *mg/dL*	1.5 (1–1.7)	1.25 (1.1–2.1)	.12	0.7 (0.65–0.85)	0.7 (0.62–0.082)	.86
eGFR, *mL/min/1.73 m*^{2}	90 (53–90)	90 (65–90)	.20	90 (81–90)	90 (83–90)	.46
Prednisone, *mg/d*	10 (5–30)	0 (0–3.7)	.01	-	-	
Complete clinical response, n (%)	-	25 (71)				
BVAS v3 score	9 (4–12)	3 (0–6)	.001	-	-	
Clinical manifestations, n (%)						
Purpura	23 (65)	2 (6)	.01			
Arthralgia	11 (31)	1 (3)	.01			
Weakness	25 (70)	1 (2)	.01			
Polyneuropathy	18 (50)	5 (14)	.01			
Renal involvement	7 (20)	2 (5)	.02			
Hematuria >10 RBCs/hpf, n (%)	5 (71)	2 (25)	.03			
Median eGFR, *mL/min/1.73 m*^{2}	40 (31–44)	54 (36–60)	.03			
Proteinuria, *g/L*	1.4 (1.1–1.9)	0.17 (0.9–1.8)	.73			
Creatinine level, *mg/dL*	1.6 (1–1.7)	1.27 (1.1–2)	.89			

associated with CIR (odds ratio, 9.8; 95% confidence interval, 2.2–44; P (.03)

The median duration of follow-up after DAAs was 24 (17-41) months

Lens S et al 2017

Virologic, Clinical, and Immune Response Outcomes of Patients With Hepatitis C Virus–Associated Cryoglobulinemia Treated With Direct-Acting Antivirals

Birmingham Vasculitis Activity Score version 3

(eGFR) <60 ml/min/1.73m^2, hematuria and/or proteinuria >0.3 g/24 hours,

Immunological markers included rheumatoid factor (RF), complement 4 (C4),

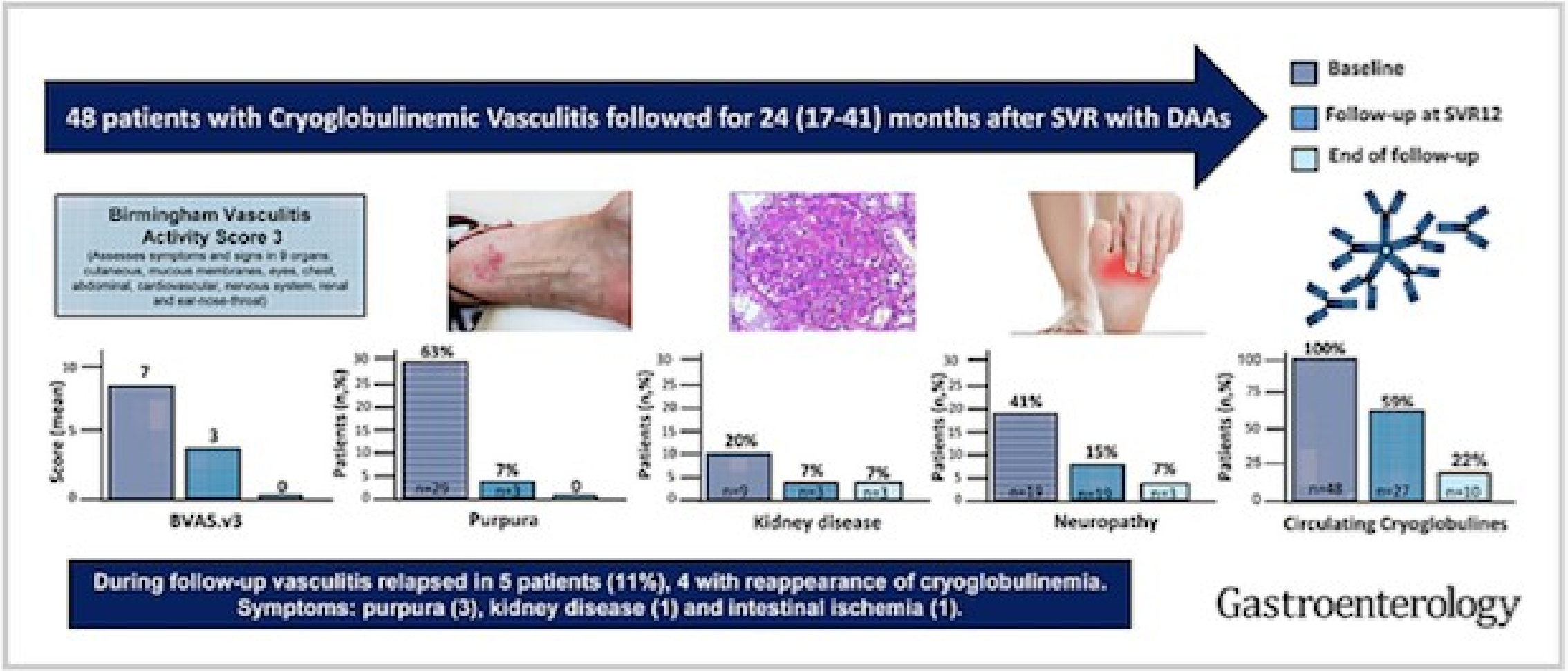
Total hemolytic complement 50 (CH50) fractions and circulating cryoglobulins levels.

Visual analogue scale, NTSS-6 score (Neuropathy Total Symptom Score-6) and electrophysiology

evaluation when necessary

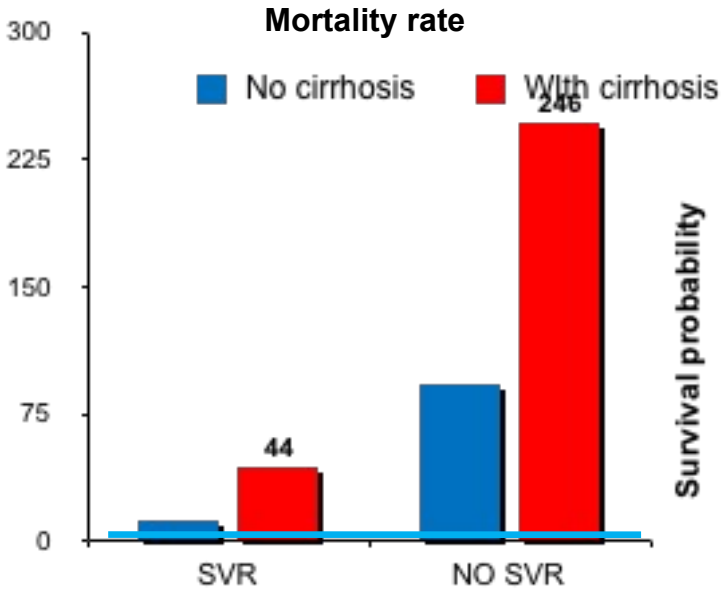
Long-Term Outcomes of Patients With HCV-Associated Cryoglobulinemic Vasculitis After Virologic Cure

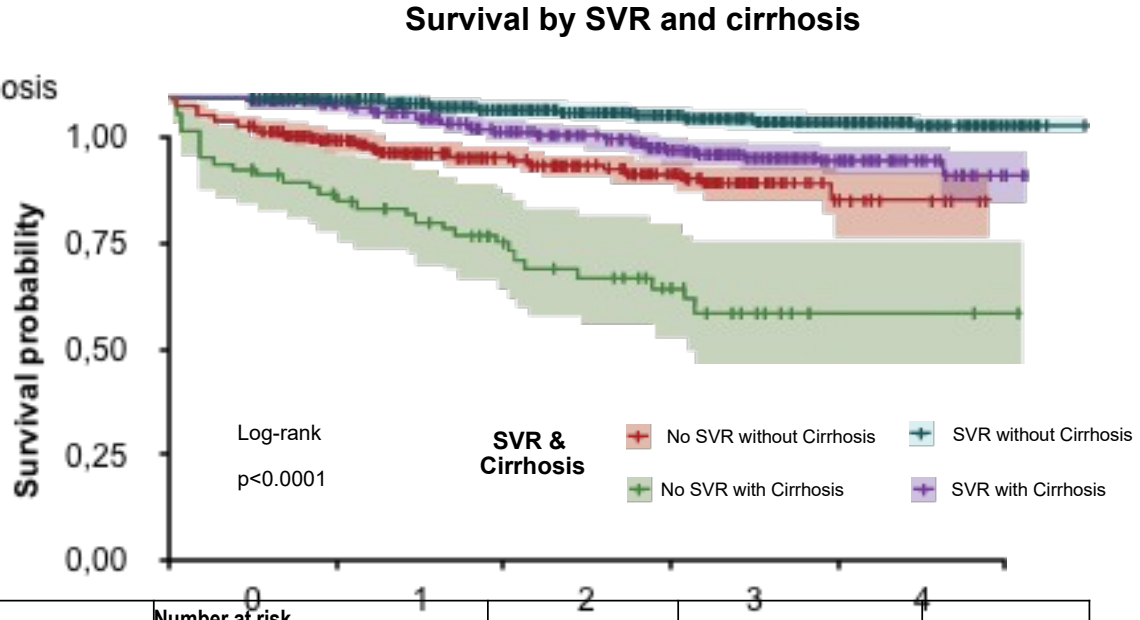
Martín Bonacci, Sabela Lens, Zoe Mariño, María-Carlota Londoño, Sergio Rodriguez-Tajes, José M. Sánchez-Tapias, Manel Ramos-Casals, José Hernández-Rodríguez, Xavier Forns



Achieving SVR improves patient survival in the real world (BC hepatitis testers cohort, Canada)

- Impact of DAAs on mortality reduction among those with and without cirrhosis in a population-based cohort in Canada





	Number at risk		Person Years at Risk		
No SVR without Cirrhosis	473	270	148	40	4
No SVR with Cirrhosis	77	49	30	10	3
SVR without Cirrhosis	5993	4823	3102	959	93
SVR with Cirrhosis	583	533	417	174	22

Both DAA and IFN-based SVR substantially reduce all-cause mortality, with lower reductions in those with cirrhosis

Janjua NZ, et al. AASLD 2018; Oral #145

Conclusions

DAA induced SVR is durable and substantially reduces all-cause mortality

In patients without significant fibrosis no further monitoring is required

In patients with F3-F4 fibrosis post SVR12 monitoring requires HCC surveillance and EGD

In patients with HCV-related extra hepatic manifestation long-term monitoring of renal function, cryocrit and neurological manifestation is required

Virologic, Clinical, and Immune Response Outcomes of Patients With Hepatitis C Virus–Associated Cryoglobulinemia Treated With Direct-Acting Antivirals

88 consecutive HCV-infected patients with CC. Among them, 46 (53%) [51] accomplished criteria of HCV-CV[7,8], and 42 (47%) had ACC.

Among HCV-CV patients, the main clinical manifestations were purpura (63%), weakness (61%), neuropathy (41%), and nephropathy (20%).

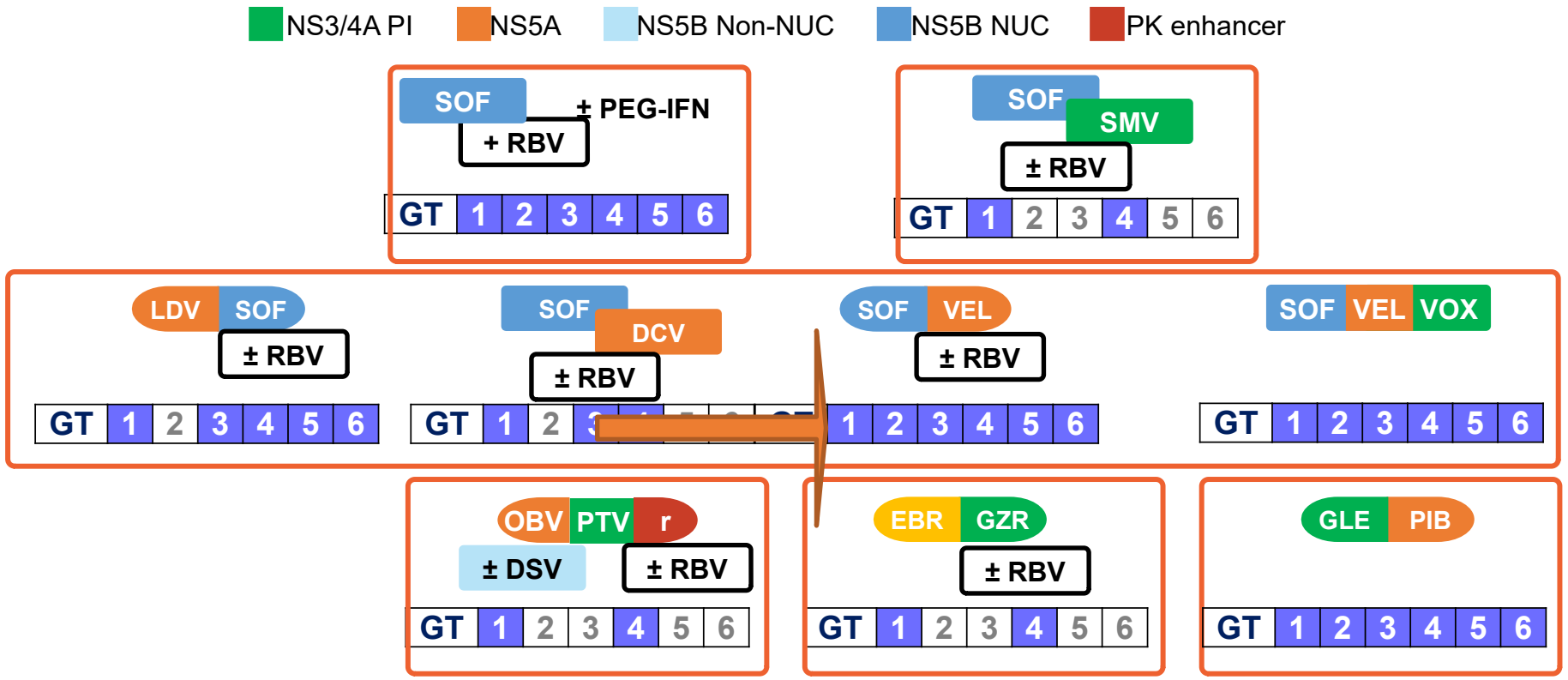
Cryocrit and RF levels were significantly higher in HCV-CV compared to ACC patients (2.8% *vs*. 2.3%, p=0.04 and 50 IU/mL *vs*. 10 IU/mL, p=0.01, respectively)

	Baseline	FU at PT12	Last-FU	p
Follow-up (months)			24(17-42)	
Cryocrit (%)	2.8 (1.3-5.7)	0.6 (0-1.4)	0 (0-0.6)	0.01
Circulating cryoglobulins n(%)	46(100)	27(59)	10(22)	-
Serum C4 level (g/L)	0.04 (0.01-0.10)	0.11(0.05-0.15)	0.14(0.08-0.17)	0.01
Abnormal C4 n(%)	36(78)	24(52)	10(22)	-
Serum CH50 level (U/mL)	15(12-26)	33(11-46)	52(41-55)	0.01
Abnormal CH50 n(%)	35(76)	15(33)	8(17)	-
Rheumatoid factor level(IU/mL)	50 (12-230)	20(10-60)	15 (10-47)	0.04
AbnormalRheumatoid factor n(%)	33(71)	21(45)	9(20)	-
Complete Immunologic response n(%)	-	18(39)	30(66)	
Creatinine level(mg/dl)	1.4 (1-1.6)	1.3 (0.9-1.9)	1.1 (0.8-1.5)	0.86
eGFR(ml/min/1.73m²)	90(53-90)	90(65-90)	90 (81-90)	0.46
Prednisone (mg/day)	15(5-30)	0 (0-5)	0(0-2.5)	
Patients under prednisone n(%)	19(41)	8(17)	4(9)	
Complete clinical response n(%)**	-	32(70%)	37(80%)	
BVAS v3 score*	7 (2-31)	3 (0-11)	0 (0-8)	0.01
Clinical manifestations n(%)				
Purpura/Arthralgia/Weakness	29(63)/16(35)/28(61)	3(7)/1(2)/1(2)	0	
Polyneuropathy	19(41)	7 (15)	3(7)	
Renal involvement	9(20)	3(7)	3(7)	
Creatinine levels (mg/dl)	1.7(1-1.8)	1.3(1.1-2)	1.2(0.8-2.3)	
eGFR(ml/min/1.73m²)	42(30-46)	52(34-59)	49(28-70)	
Hematuria >10RBCs/hpf	7(78)	3(33)	3 (33)	
Proteinuria (g/l)	1.5(1.1-1.8)	0.2(0.1-2.1)	0.2(0.1.-1.9)	

Bonacci et al Gastroenterology 2017

The median duration of follow-up after DAAs was 24 (17-

We have now the tools to successful treating the vast majority of patients with HCV infection

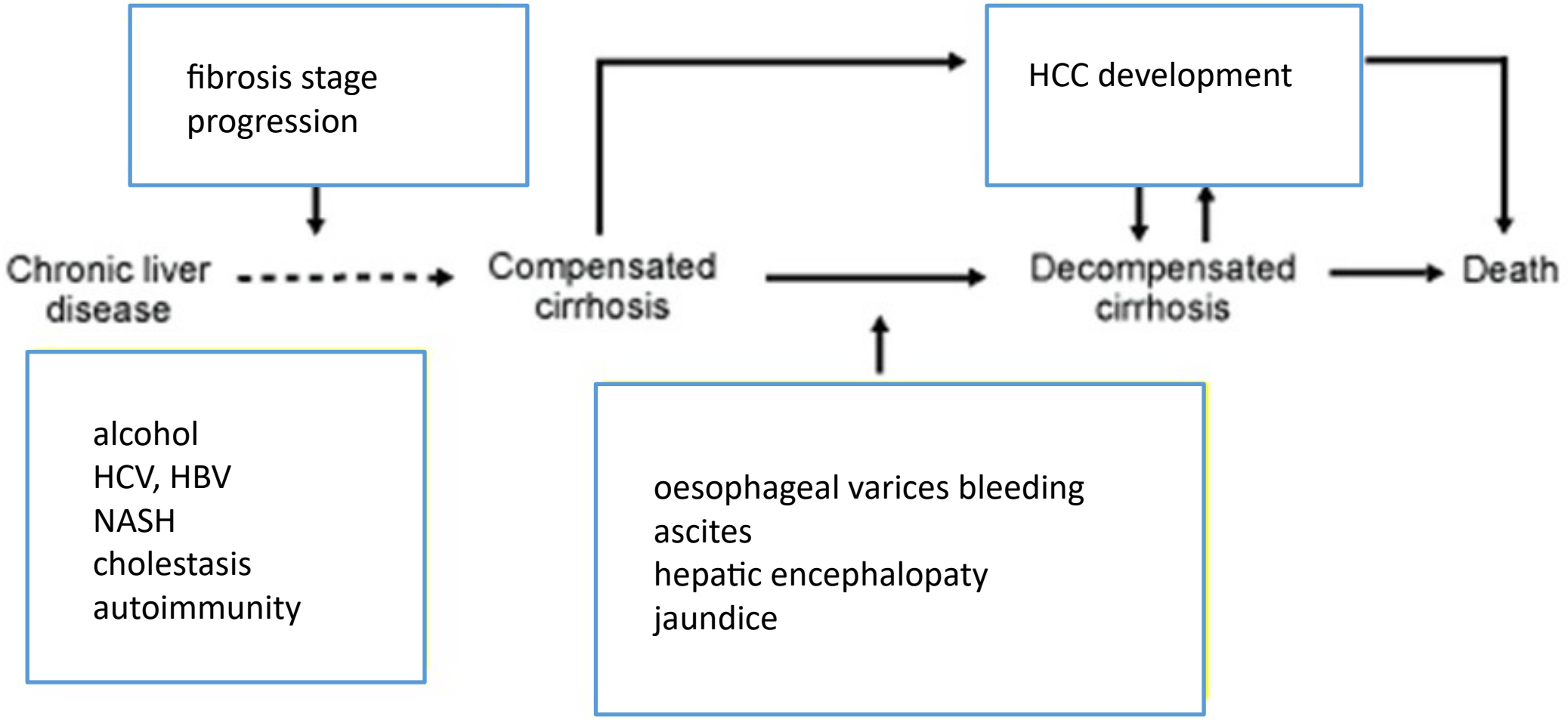


Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir) SmPC, October 2017; Janssen-Cilag Ltd. OLYSIO▼ (simeprevir) SmPC, August 2017; Bristol-Myers Squibb Pharma EEIG. DAKLINZA▼ (daclatasvir) SmPC, March 2017; Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir) SmPC, December 2017; AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir) SmPC, November 2017; AbbVie Ltd. EXVIERA▼ (dasabuvir) SmPC, December 2017; Gilead Sciences Europe Ltd. EPCLUSA▼ (sofosbuvir/velpatasvir) SmPC, October 2017; Merck Sharp & Dohme Ltd. ZEPATIER▼ (grazoprevir/elbasvir) SmPC, May 2017; Gilead Sciences Europe Ltd. VOSEVI▼ (sofosbuvir/velpatasvir/voxilaprevir) SmPC, September 2017; AbbVie Ltd. MAVIRET▼ (glecaprevir/pibrentasvir) SmPC, August 2017

Long-term effect of DAA therapy in patients with HCV infection

- Does portal hypertension improve?
- Do extra-hepatic manifestations of HCV improve?

Natural history of chronic liver diseases



HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis.

Post-treatment monitoring

- SVR and normal ALT in non cirrhotic patients = patient cured without need of clinical follow-up for HCV
- SVR and abnormal ALT in non cirrhotic patients = patient in need of specialized evaluation aimed at excluding liver diseases
- SVR and cirrhosis = patient in need of bi-annual visit and monitoring, including enrolment in screening programs for HCC , esophageal varies and osteoporosis

Conclusioni

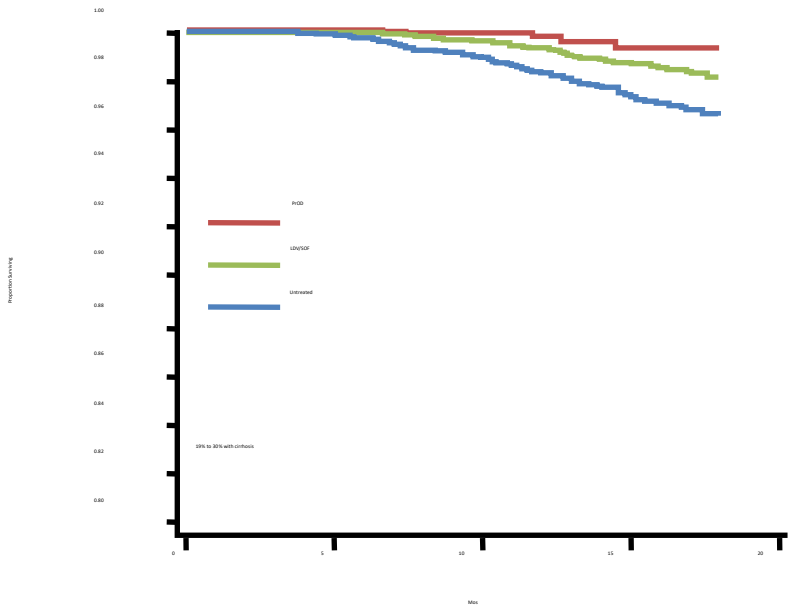
Il trattamento per l'epatite C con DAA ha dimostrato che l'infezione si può curare in alcune popolazioni fragili inclusi i pazienti con emoglobinopatie

Il trattamento con SOF/LDV dei pazienti con talassemia major ha dimostrato che l'infezione può essere eradicata anche nei cirrotici senza la necessità di RBV e dopo terapia di soli 12 mesi con 98% di SVR

L'obiettivo della terapia è la SVR cioè HCV RNA non rilevabile 12 settimane dopo la fine della terapia equivale alla guarigione

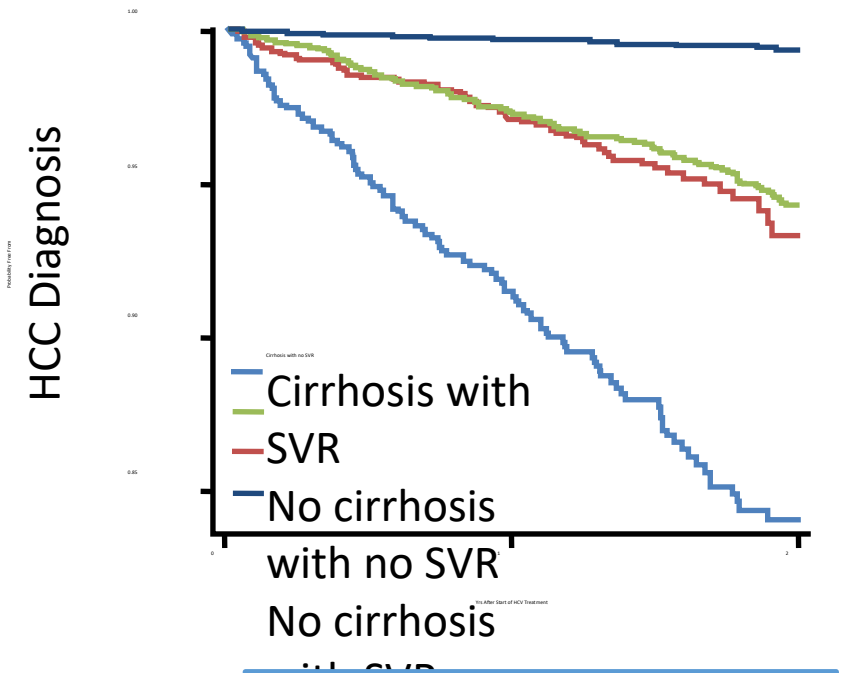
Il monitoraggio post terapia deve differenziarsi per pazienti non cirrotici e cirrotici/pazienti con fibrosi avanzata (F3/F4)

†)[1]



DAA-induced SVR is associated with a 43% reduction in mortality

‡)[2]



DAA-induced SVR is associated with a 71% reduction in HCC

*For 18 mos of follow-up.

†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.

For 38,204 pt-yrs of follow-up.

1. Butt AA, et al. Clin Infect Dis. 2017:65:1006-1011.

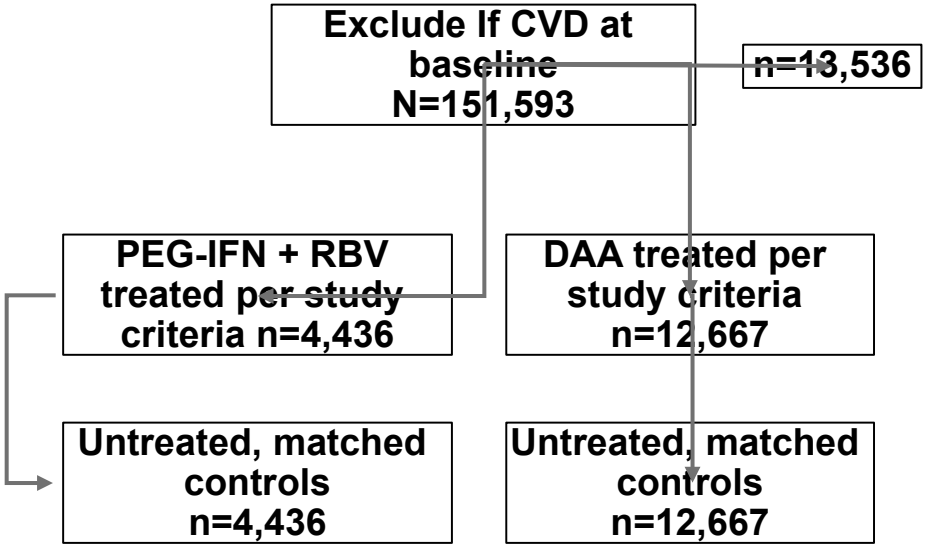
2. Ioannou GN, et al. J Hepatol. 2017;[Epub ahead of print].

HCV treatment reduces incidence of cardiovascular events (ERCHIVES VA HCV database)

Baseline characteristics

	Treated n=17,103	Untreated n=17,103
Age, median	59	58
Race, %		
White	56	56
Black	24	24
Male, %	96	96
Alcohol abuse/ dependence, %	37	41
Drug abuse/ dependence, %	36	40
BMI, % >30 kg/m^2	35	29
FIB-4 >3.25, %	21	17
Median total cholesterol, mg/dL	165	170
Diabetes, %	8	9
Hypertension, %	51	54
SVR, %	76	–

Study flow

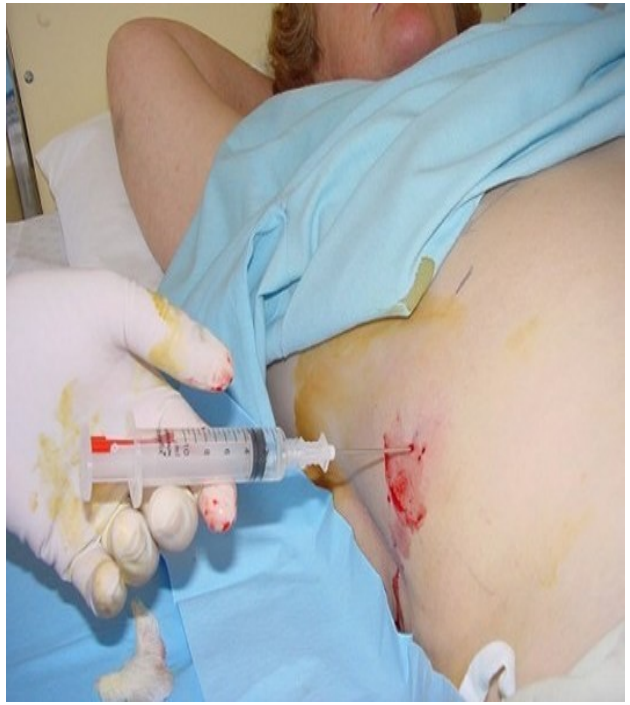


CV Events: Acute myocardial infarction, angina, cardiac failure, peripheral vascular disease, bypass, angioplasty, stroke

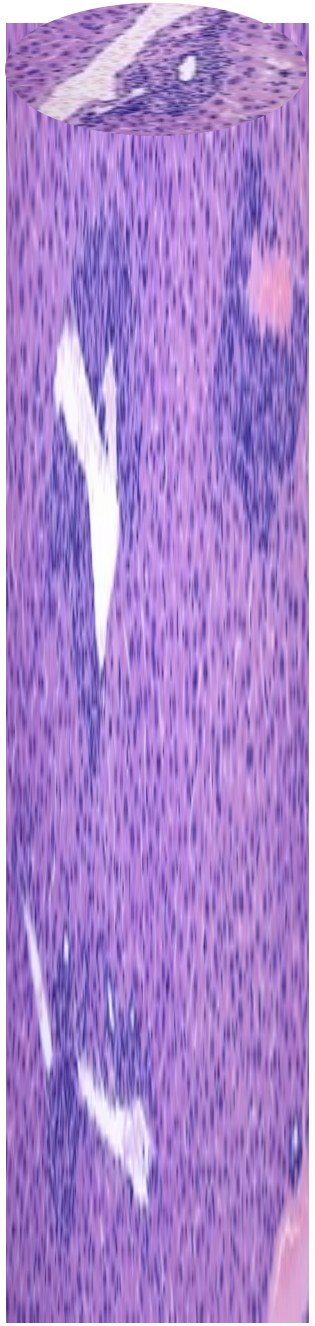
Butt AA, et al. AASLD 2018; Poster #1566

How to monitor our SVR patients with
portal hypertension?
risk of HCC
compensated cirrhosis?

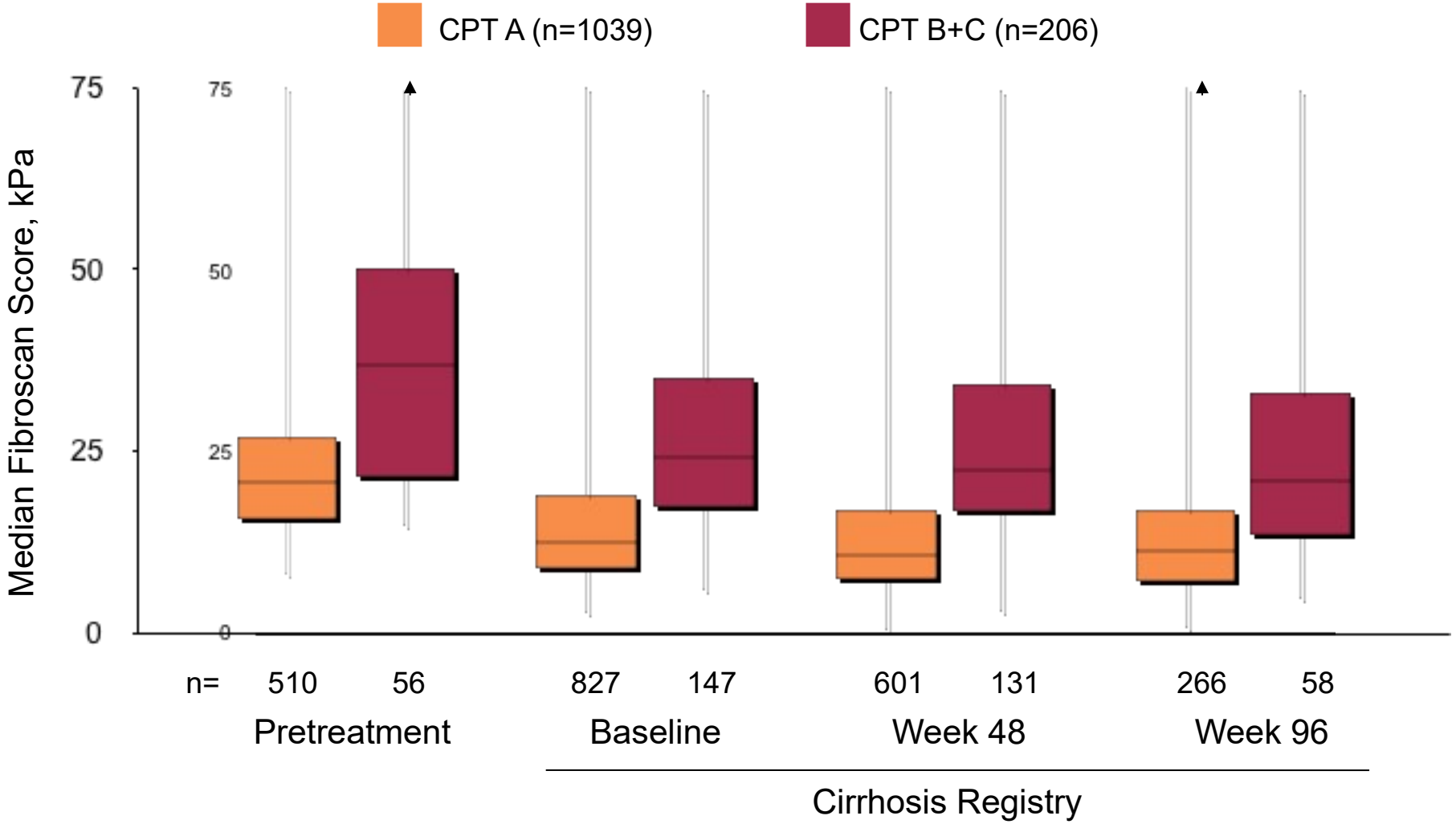
Liver biopsy is an invasive technique



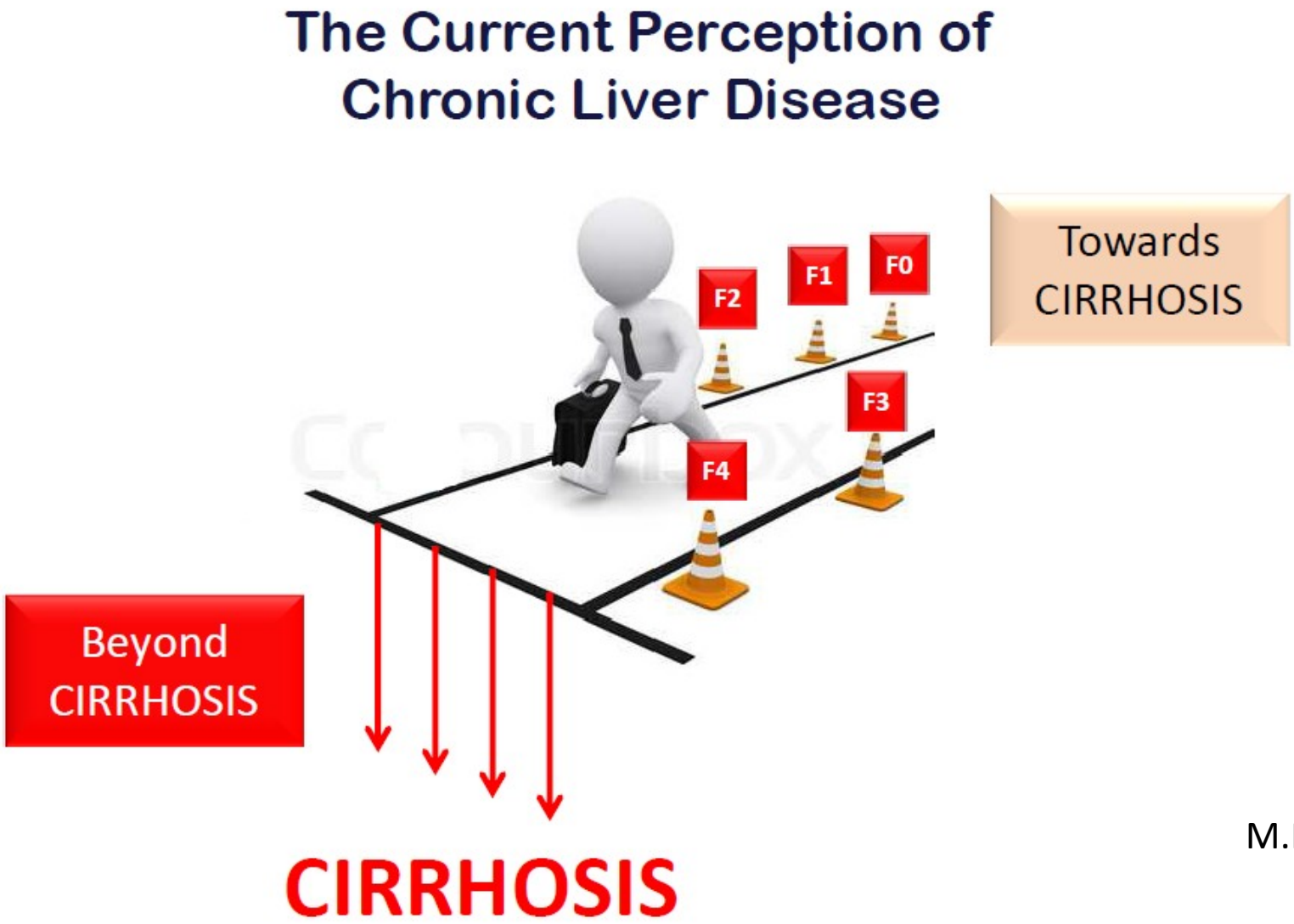
- "the best possible reference standard"
- morbidity:significant bleeding < 0.7%
- mortality< 0.03%



Results: Median Fibroscan Results Over Time



Natural history of chronic liver diseases



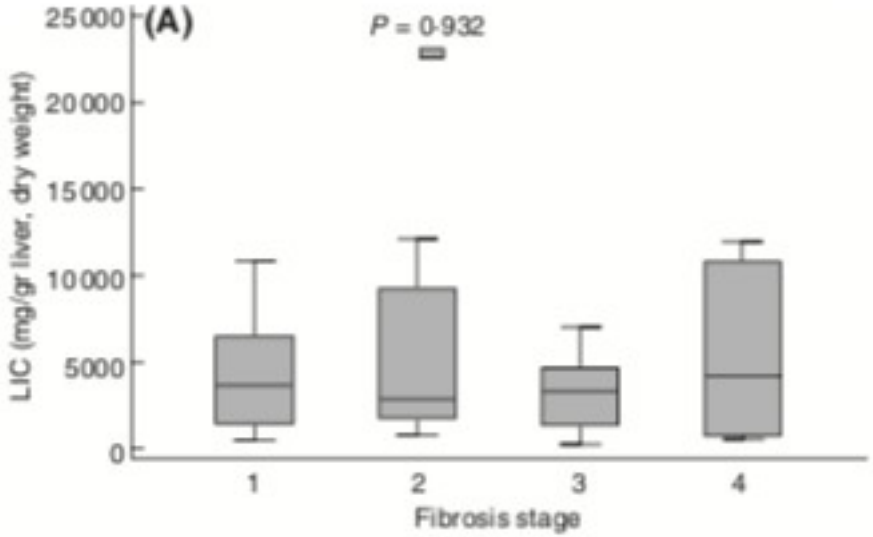
M.Pinzani 2012

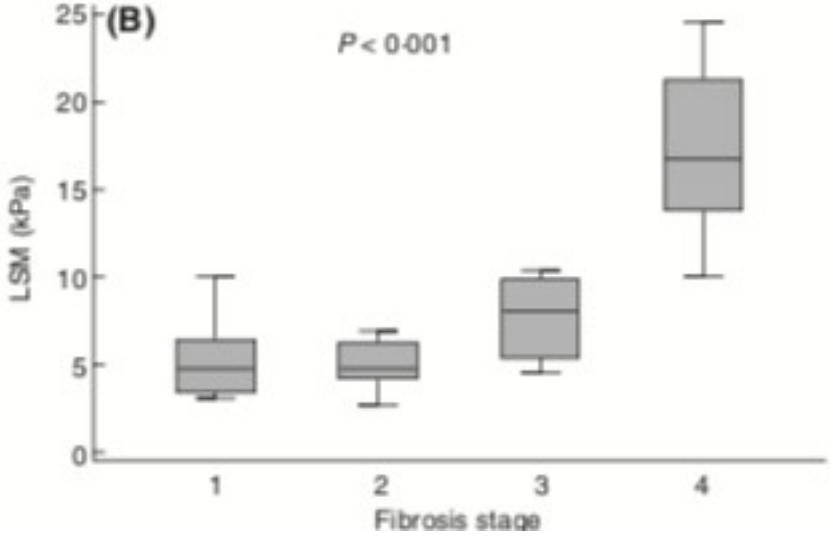
SVR means….

- SVR = undetectable HCV RNA in serum or plasma by PCR 12 weeks after the end of treatment with DAA
- Late relapse is rare <0.5%. Re-infection may be the cause of a detectable HCV RNA in patients previously undetectable in 0.1-02% of cases
- Non cirrhotic patients with normal liver enzymes after SVR do not need further follow-up and can be considered as uninfected
- No reasons to repeat HCVAb testing as HCVAb persists and does not indicate active infection or protect against a possible new infection

Is fibroscan reliable to assess liver fibrosis in patients with thalassemia major?

Short Report





British Journal of Haematology,2009, 148, 476–479

Factors Associated With End of Treatment Alanine Aminotransferase Elevation in Patients Treated With Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir

Tania Welzel,[1] Paul Y. Kwo,[2] Ira M. Jacobson,[3] Jie Zhang,[4] Brian McNabb,[4] John McNally,[4] Diana M. Brainard,[4] John G. McHutchison,[4] Keyur Patel,[5] Mark S. Sulkowski,[6] Graham R. Foster[7]

[1]Medizinische Klinik 1, Universitätsklinikum Frankfurt, Germany; [2]Stanford University School of Medicine, Stanford, CA; [3]Mount Sinai Beth Israel, New York, NY; [4]Gilead Sciences, Inc., Foster City, CA; [5]Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada; [6]Johns Hopkins University, Baltimore, MD; [7]Queen Mary University of London, UK

Demographics and Medical History

	Elevated EOT ALT n=767	Normalized EOT ALT n=2248
Mean age, y (SD)	53 (10)	53 (10.5)
Mean BMI, kg/m^2 (range)	28 (18–57)	27 (17–61)
Male, n (%)	364 (48)	1402 (62)
White, n (%)	637 (83)	1875 (83)
Treatment naïve, n (%)	104 (81)	137 (72)
Compensated cirrhosis, n (%)	233 (30)	257 (11)
Concomitant treatment with, n (%)		
Diabetes medication	91 (12)	136 (6)
HMG-CoA reductase inhibitor (statin)	39 (5)	103 (5)
Medical history of, n (%)		
Diabetes	119 (16)	181 (8)
Hypertension	311 (41)	718 (32)
Dyslipidemia	80 (10)	214 (10)

BMI, body mass index; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; SD, standard deviation.

Univariate Logistic Regression Assessing Factors Associated With Elevated EOT ALT

Variable	OR (95% CI)	p-Value
Age, /10-y increase	1.05 (0.97, 1.14)	0.20
BMI, /5-kg/m^2 increase	1.31 (1.21, 1.41)	<0.001
Weight gain during treatment, /1-kg increase	1.02 (0.99, 1.06)	0.13
Female	1.84 (1.56, 2.17)	<0.001
Compensated cirrhosis	3.37 (2.75, 4.12)	<0.001
Concomitant treatment with:		
Diabetes medication	2.09 (1.58, 2.74)	<0.001
HMG-CoA reductase inhibitor (statin)	1.12 (0.76, 1.63)	0.60
Medical history of:		
Diabetes	2.1 (1.64, 2.69)	<0.001
Hypertension	1.45 (1.23, 1.72)	<0.001
Dyslipidemia	1.12 (0.84, 1.45)	0.50
HCV RNA, /1-$\log_{10}$ IU/mL increase	0.92 (0.81, 1.03)	0.16
HbA1c, /1% (absolute) increase	1.43 (1.26, 1.62)	<0.001
Random glucose, /1-SD (28.7 mg/dL) increase	1.28 (1.18, 1.38)	<0.001

CI, confidence interval; OR, odds ratio.

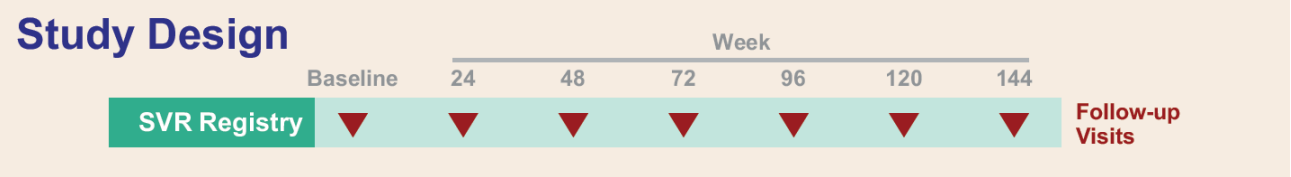
Multivariate Logistic Regression Identifying Independent Factors Associated With Elevated EOT ALT

Variable	OR (95% CI)	p-Value
BMI, /5-kg/m^2 increase	1.23 (1.13, 1.34)	<0.001
Female	2.22 (1.86, 2.65)	<0.001
Compensated cirrhosis	3.28 (2.65, 4.05)	<0.001
Medical history of:		
Diabetes*	1.36 (0.98, 1.89)	0.07
Hypertension	1.18 (0.98, 1.42)	0.09
HbA1c, /1% (absolute) increase*	1.2 (1.01, 1.42)	0.04

*Medical history of diabetes was colinear with use of diabetes medication and HbA1c was colinear with random glucose (p <0.001); so glucose and use of diabetes medications were left out of final model.

Gilead SVR registry: long-term outcomes from >6600 patients treated with SOF-based regimens

- 3-year registry study of patients treated in Gilead-sponsored trials who achieved SVR§



	SOF+ RBV ± PEG-IFN (n=1724)	LDV/SOF ± RBV (n=2204)	SOF/VEL ± RBV (n=1422)	SOF/VEL/VOX (n=597)	Other (n=660)	Total (N=6607)
Mean age, y (range)	52 (19–76)	55 (19–83)	55 (20–82)	56 (23–82)	51 (20–76)	54 (19–83)
Male, n (%)	1117 (65)	1404 (64)	844 (60)	364 (61)	373 (57)	4102 (62)
Race/ethnicity* White Hispanic/Latino	 1489 (86) 203 (12)	 1843 (84) 217 (10)	 1194 (84) 128 (9)	 486 (81) 52 (9)	 562 (85) 69 (10)	 5574 (84) 669 (10)
Cirrhosis, n (%)	349 (20)	526 (24)	200 (14)	51 (9)	61 (9)	1187 (18)**
IL28B CC, n (%)	613 (36)	500 (23)	431 (30)	157 (26)	259 (39)	1960 (30)
HCV genotype, n (%) 1 / 2 / 3 / 4 / 5 / 6 / other†	 (44) / 70 (4) / 1 (<1) / 3 (<1) / 0	 (1) / 23 (1) / 3 (<1) / 5 (<1)	 (27) / 109 (8) / 27 (2) / 37 (3) / 0	 340 (57) / 64 (11) / 108 (18) / 49 (8) / 14 (2) / 19 (3) / 3 (<1)	 651 (99) / 3 (<1) / 6 (<1) / 0 / 0 / 0 / 0	 4233 (64) / 695 (11) / 1289 (20) / 255 (4) / 65 (1) / 62 (<1) / 8 (<1)

Schwabe C, et al. AASLD 2018; Poster #595

§Sustained virological response at last visit. *Based on data collected from treatment studies; **Among patients with cirrhosis, mean CTP score at baseline was 5.2 (range 5–10); †Mixed/indeterminate/missing.
CTP: Child–Turcotte–Pugh; LDV: ledipasvir; PEG-IFN: interferon; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

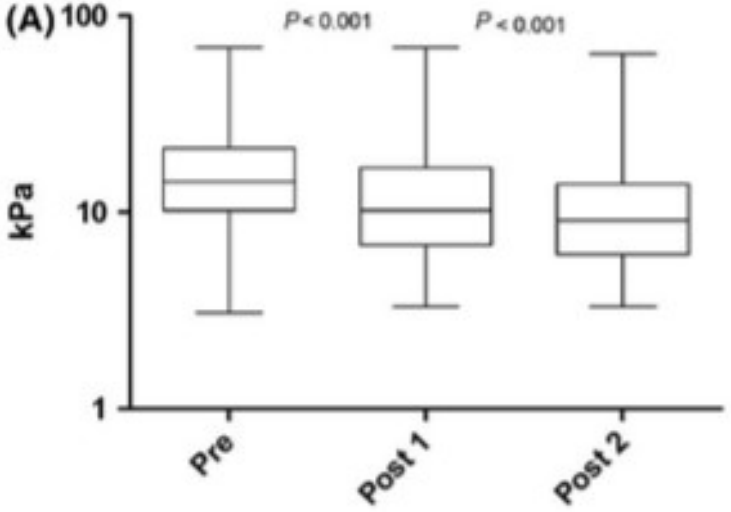
Gestione a lungo termine dei pazienti con malattia epatica

- I soggetti la cui funzione epatica rimane anormale dopo la SVR devono essere valutati da uno specialista epatologo
- Tutti i cirrotici devono essere inclusi in un programma di sorveglianza per l'epatocarcinoma secondo le raccomandazioni delle linee guida
- Le complicanze della cirrosi inclusa la malnutrizione e l'osteoporosi devono essere valutate e gestite da specialisti

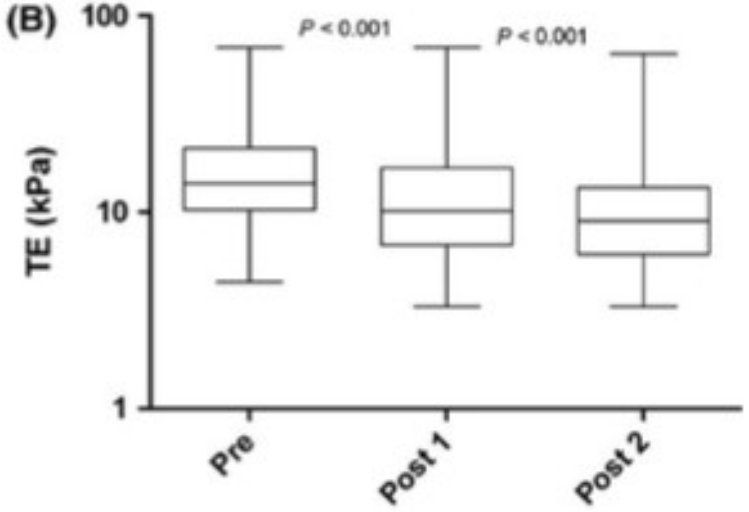
La fibrosi migliora dopo la terapia?

Banchofer E et al Liver Intern 2017

Tutti i pazienti



Pazienti con SVR



Pazienti non responder