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PARIS - Palais des Congrès

International Conference on the Management of Patients with Viral Hepatitis

Why do I treat my patients with mild hepatitis C?

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Grant/Research Support: Abbvie, BMS, MSD, Roche,

Consultant/Advisor: Abbvie, Abbott, Achillion, Boehringer Ingelheim, BMS, Gilead, Janssen-Cilag, MSD, Novartis

Sponsored lectures: Abbvie, BMS, Gilead, Janssen-Cilag, MSD

Treatment prioritization

EASL Recommendation on HCV management, J HEP 2015; 63: 199

Treatment priority	Patient group
Treatment should be prioritized	. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis . Patients with HIV coinfection . Patients with HBV coinfection . Patients with an indication for liver transplantation . Patients with HCV recurrence after liver transplantation . Patients with clinically significant extra-hepatic manifestations . Patients with debilitating fatigue . Individuals at risk of transmitting HCV
Treatment is justified	. Patients with moderate fibrosis (F2)
Treatment can be deferred	. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	. Patients with limited life expectancy due to non-liver related comorbidities

AASLD/IDSA 2015: when and in whom to initiate HCV therapy

- ALL pts are candidates for HCV therapy, regardless of disease stage

- In regions *where limited resources preclude treatment of all patients*, the following groups should be prioritized for therapy:
  - Highest Priority (based on highest risk for disease complications)
    - Advanced fibrosis (F3) or compensated cirrhosis (F4)

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American Association for the Study of Liver Diseases AASLD

COMMENTS FROM THE EDITORS

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The New Hepatitis C Virus Bottleneck: Can Delaying Therapy Be Justified?

F0-F2 patients are not universally covered by insurance schemes

AASLD/IDSA. HCV Management. http://www.hcvguidelines.org.

Why should I treat my patients with mild hepatitis C?

- Available therapies are highly effective and safe
- Disease staging is not faultless
- HCV causes significant extra-hepatic morbidity
- Best cost-effectiveness is obtained treating at an early stage of disease

Why should I treat my patients with mild hepatitis C?

- Available therapies are highly effective and safe
  - Excellent SVR and safety in phase 3 and real-life cohorts
  - 8 weeks of therapy are as effective as 12
  - Modest need for retreatment if SVR > 95%
  - Ultra-short regimens (< 4 weeks) may be feasible

Genotype 1 treatment naïve non- cirrhotic: current regimens

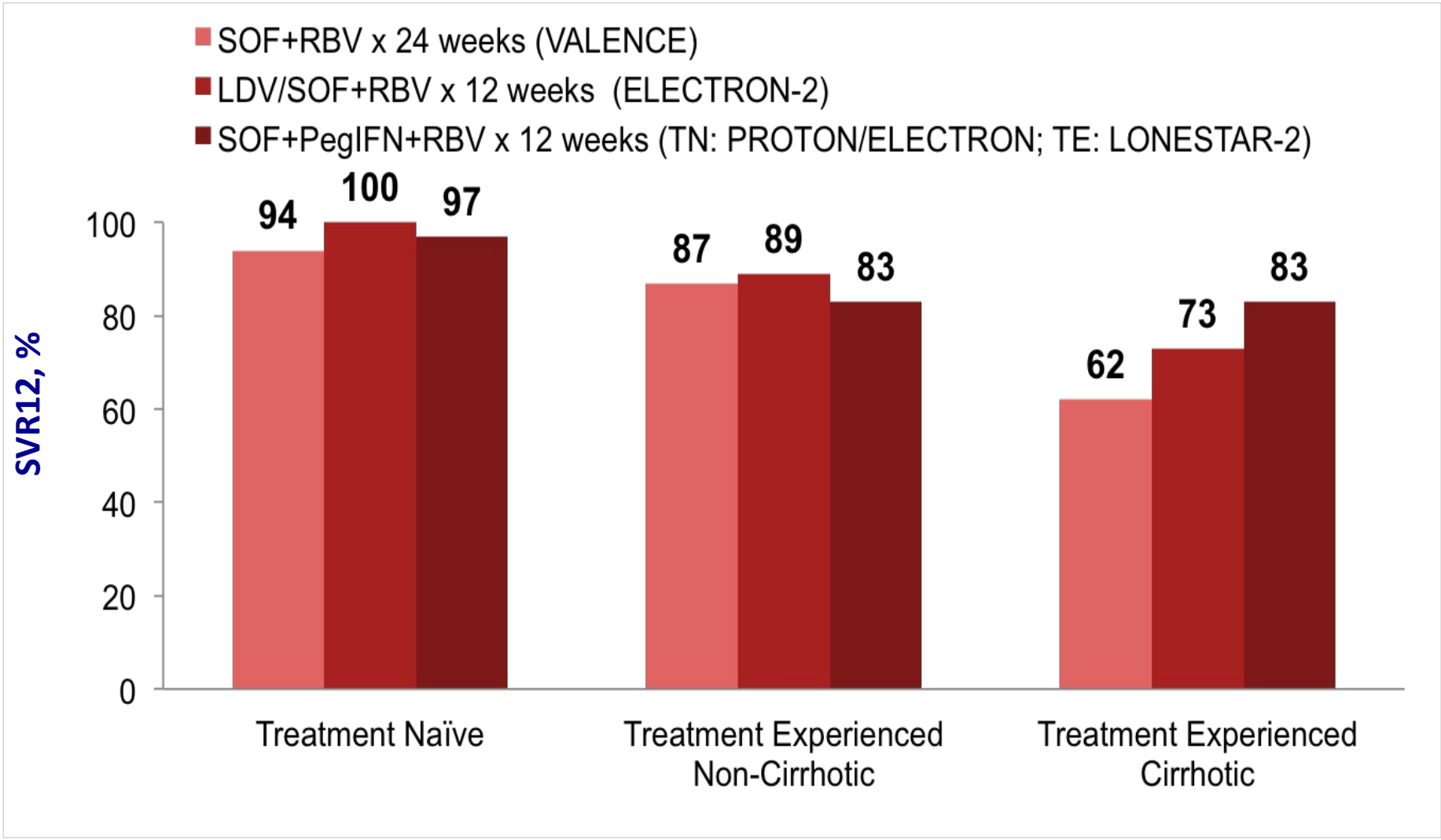
Regimen	Wks	Study	SVR
Ledipasvir/sofosbuvir (HCV RNA < 6 M IU/mL)	8	ION-3[1,2]	119/123 (97%)
Ledipasvir/sofosbuvir	12	ION-3[1]	206/216 (95%)
Simeprevir + sofosbuvir*	8-12	OPTIMIST-1[3]	8 wks: 128/155 (83%) 12 wks: 150/155 (97%)
Ombitasvir/paritaprevir/ritonavir, dasabuvir (GT1b)	12	PEARL III[4]	207/209 (99%)
Ombitasvir/paritaprevir/ritonavir, dasabuvir, ribavirin (GT1a)	12	PEARL IV[4]	97/100 (97%)
Sofosbuvir + daclatasvir	12	AI444040[5]	41/41 (100%)

*GT1a + Q80K-8 wks: 36/49 (73%); GT1a + Q80K-12 wks: 44/46 (96%).

1. Kowdley K, et al. N Engl J Med. 2014;370:1879-1888. 2. Ledipasvir/sofosbuvir [package insert].
3. Kwo PY, et al. EASL 2015. Abstract LP14. 4. Ferenci P, et al. N Engl J Med. 2014;370:1983-1992.
5. Sulkowski M, et al. N Engl J Med. 2014;370:211-221.

Genotype 3 non-cirrhotic: current regimens

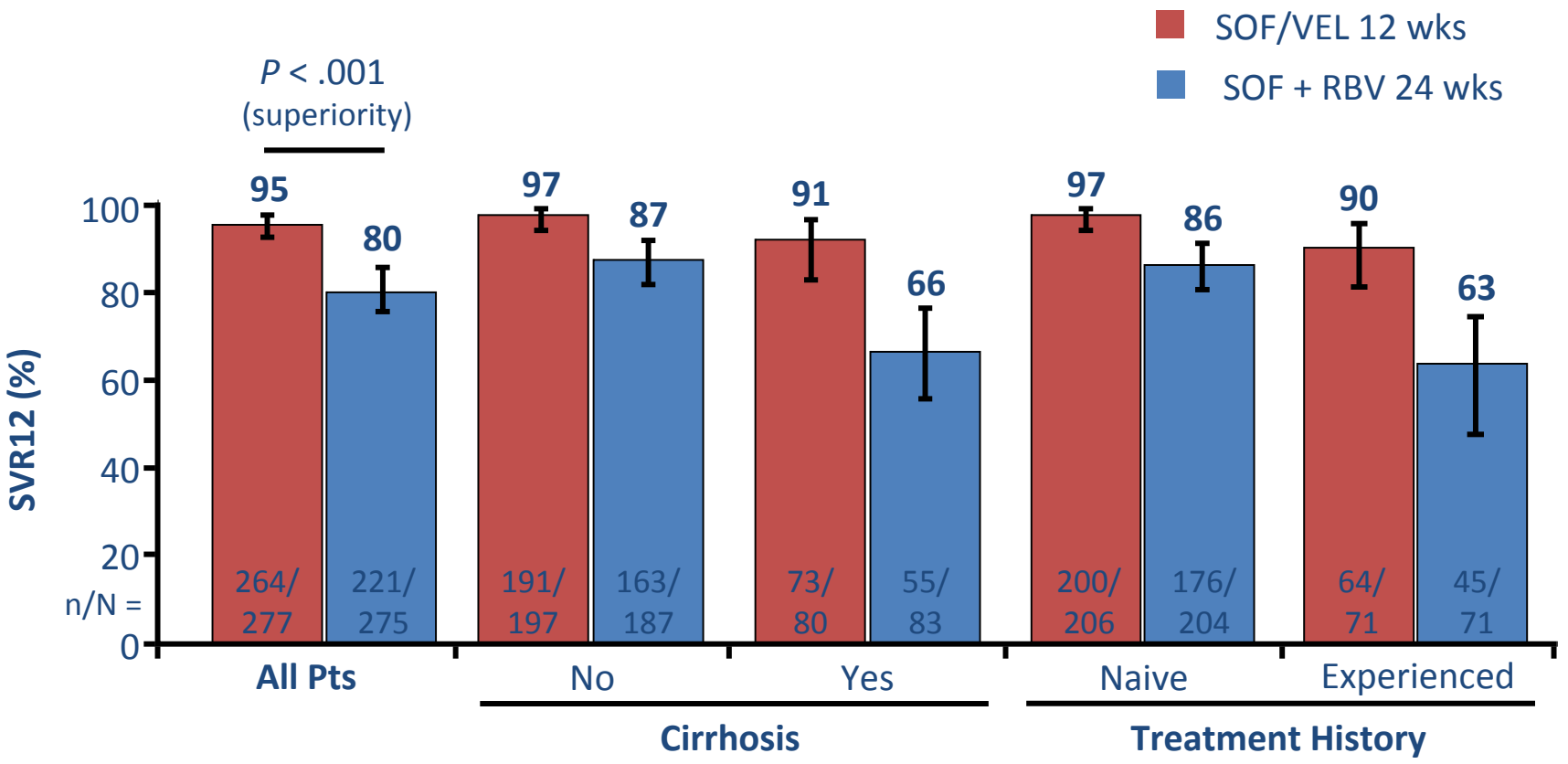
Cross-Study Comparison: VALENCE, LONESTAR-2, PROTON/ELECTRON, and ELECTRON-2



Zeuzem S, et al. *NEJM.* 2014.; Gane, EASL, 2014, Oral #6; Gane E et al. *NEJM* 2013;368:34–44; Lawitz E et al. *Lancet Infect Dis* 2013;13:401–408; Gane, AASLD, 2014, Poster #LB-11; Lawitz E, et al. *Hepatology* 2015;61:769-775

SVR12, Safety With Sofosbuvir/Velpatasvir in GT3 HCV

SVR12 rate numerically lower with vs without BL NS5A RAVs (88% vs 97%)



Mangia A, et al. AASLD 2015. Abstract 249..
Foster GR, et al. N Engl J Med. 2015;[Epub ahead of print].

Safety summary of selected DAA combinations

Parameter	Placebo n=105	LDV/SOF n=1080	LDV/SOF n=872	O/P/D n=509	O/P/D n=1551	GZR/EBR n=1,033	GZR/EBR n=657
		no RBV	+ RBV	no RBV	+ RBV	no RBV	+ RBV
≥1 AE, %	68.6	74	85	75	88	71.4	83.6
≥1 TAE, %	39.0	45	71			40.1	67.6
SAEs, %	2.9	3	2	1,4	3	2.4	2.6
Treatment-related SAEs, %	0	<1	<1			0.1	0.5
D/C due to AE, %	1.0	1	1	0.4	1	0.5	1.7
Mean Hgb decline at TW8, mg/dL	-0.1	- 0.2 ION3	-1.9 ION3			-0.3	-2.2
Grade 3+ ALT ↑, %	8.6	< 1%	<1 %	0.2	1.3	1.6	0.6
Grade 3+ increase in total bilirubin, %	0	< 1%	2.4%	0.4	5	0.3	5.9

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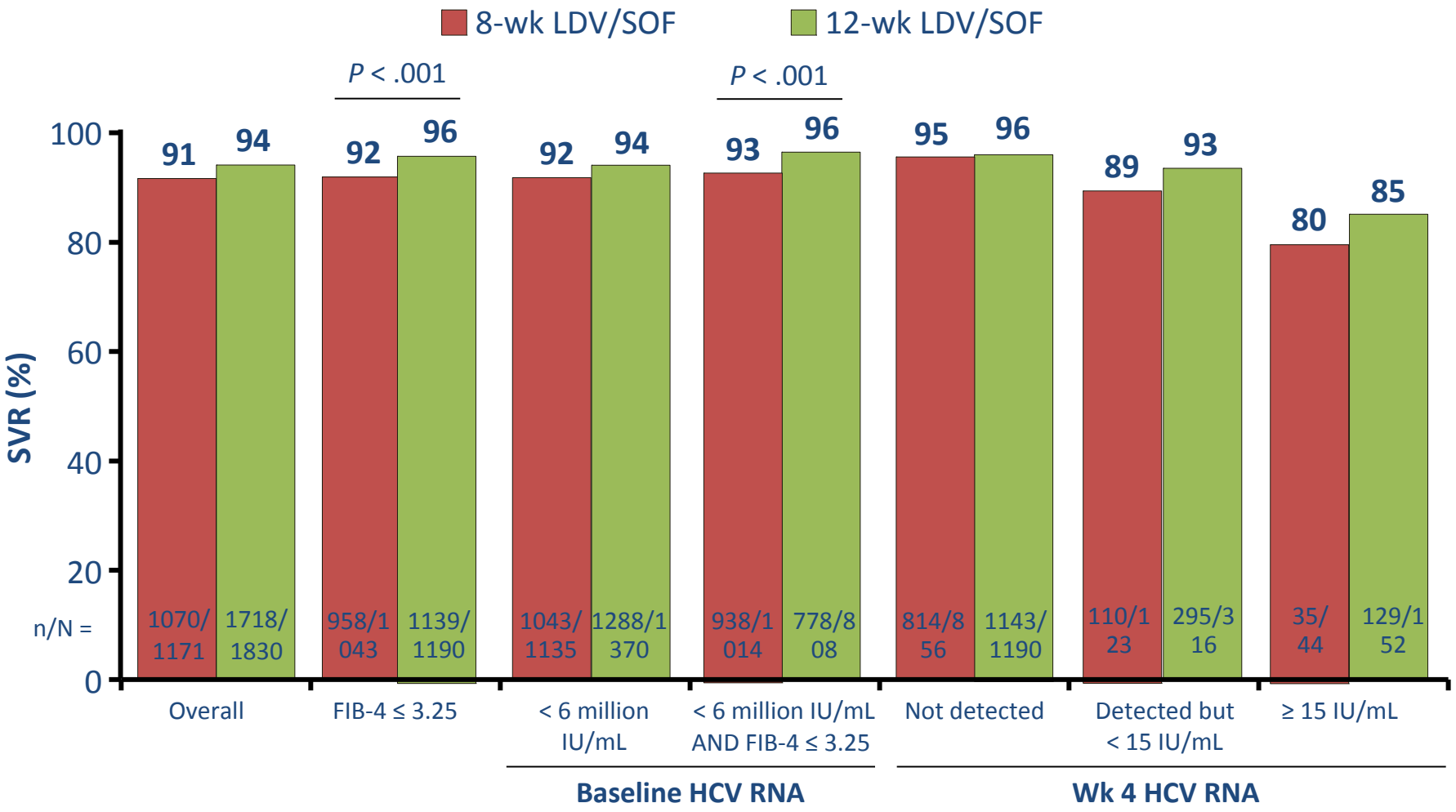
Dusheiko, AASLD 2015, 712; Kowdley KV et al. N Engl J Med. 2014 May 15;370(20):1879-88.
FDA Clinical Review NDA 205834: Ledipasvir/Sofosbuvir Fixed-Dose Combination Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000MedR.pdf
Viekira SmPC EMA (1/15); SAPPHIRE-I: Feld JJ, et al. N Engl J Med 2014;370:1594-603; SAPPHIRE-II: Zeuzem S, et al. N Engl J Med 2014;370:1604-14;
PEARL-III & PEARL-IV: Ferenci et al. N Engl J Med, 2014; 370:1983-92; PEARL-II: Andreone, P, et al. Gastroenterology 2014; 147 (2): 359-365;
TURQUOISE-II: Poordad F, et al. N Engl J Med; May 22, 2014; 370:1973-82

VA: SVR With 8-Wk vs 12-Wk Ledipasvir/ Sofosbuvir

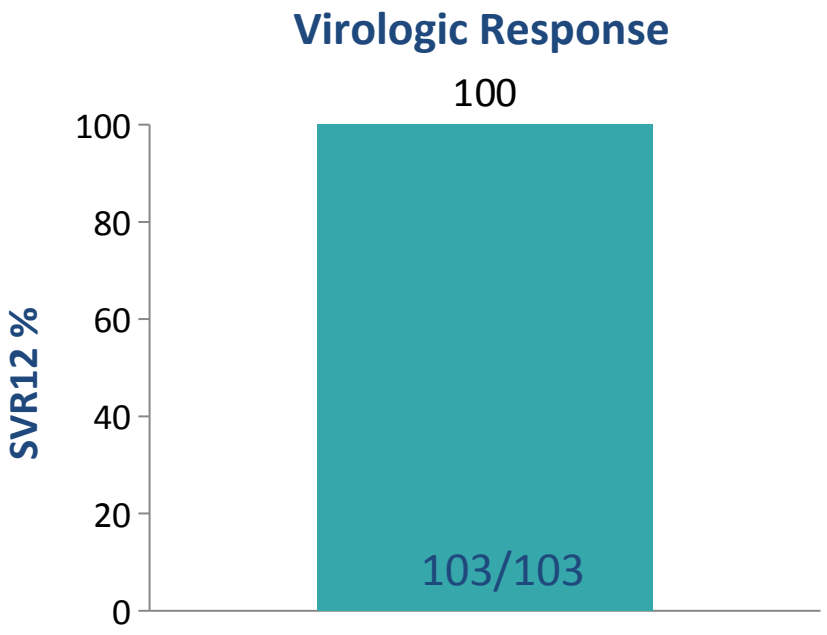


Backus LI, et al. AASLD 2015. Abstract 93.

German Real-World LDV/SOF for 8 Weeks

Single center German study of 103 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks

	N=103
Median (range) age, years	50 (22–77)
Male gender, n (%)	43 (42)
Caucasian, n (%)	103 (100)
Genotype, n (%)	
GT 1a	49 (46)
GT 1b	52 (51)
GT 4	2 (2)
Metavir stage, n (%)	
F0	56 (54)
F1	25 (24)
F2	17 (17)
F3	5 (5)
F4	0 (0)
Median baseline HCV RNA, IU/mL*	870,964
Treatment-naïve, n (%)†	100 (97)
At least one comorbidity, n (%)	94 (91)



LDV/SOF for 8 weeks resulted in high rates of SVR12 and was well tolerated

*Roche COBAS® AmpliPrep/COBAS® TaqMan®, cut-off < 12 IU/mL † including 3 PegIFN+RBV Relapsers
Fibrosis was measured by FibroScan® with cut-off values for METAVIR stage F3 or less of ≤12.3kPa.

Buggisch, AASLD, 2015, 1205.

4 or 6 weeks treatment duration for GT-1 non cirrhotic patients

6 weeks treatment

Regimen	author	SVR 12
SOF+LDV+RBV	Gane et al	68%
SOF+LDV+GS-9669	Kohli et al	95%
SOF+LDV+ GS-9451	Kholiet et al	100%
SOF + ODV (Odalasvir)	Gane et al	100%
SOF+GZR+ELB	Poordad et al	87%
SOF+VEL+GS-9857	Gane et al	93%

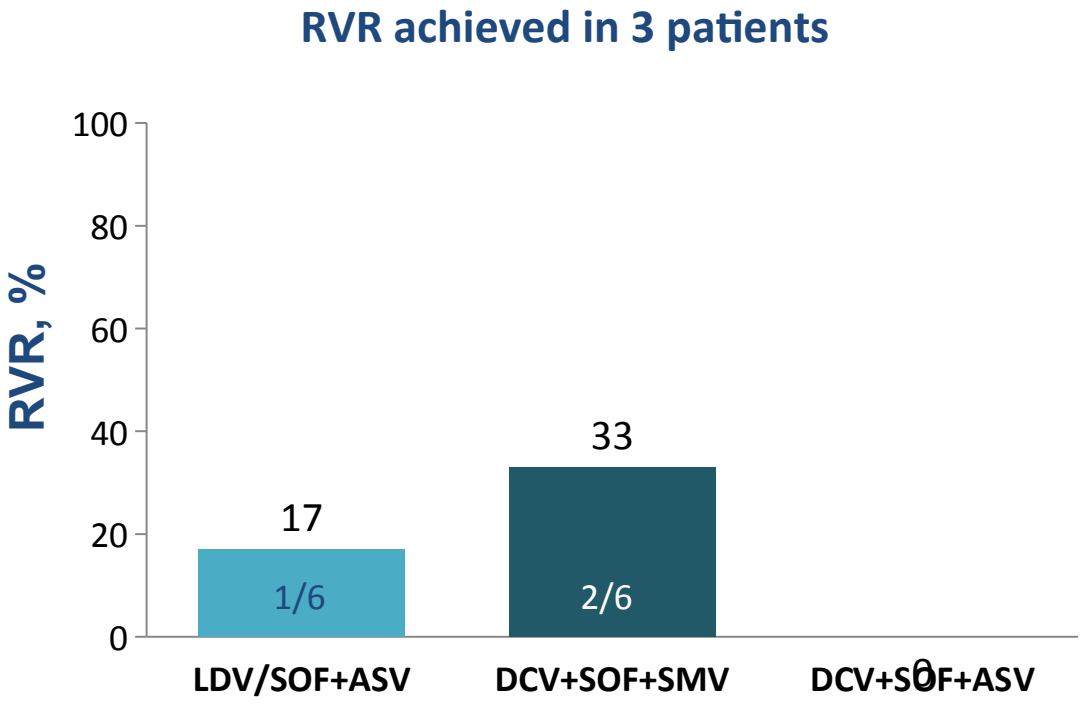
4 weeks treatment

Regimen	author	SVR 12
SOF+LDV+GS9451	Kattakuzhy et al	40%
SOF+LDV+GS-9451+GS9699	Kattakuzhy et al	20%
SOF+GZR+ ELB	Poordad et al	33 %
SOF+VEL+GS-9857	Gane et al	27%

Gane EJ, et al.Gastroenterology. 2014:146:736-43., Kohli et al, Lancet 2015, 385: 1107-1113 Kattakuzhy EASL 2015 Gane EJ et al EASL 2015, Poordad F et al. C-Swift study EASL 2015 Gane EJ et al EASL 2015

All-Oral DAA Therapy for 3 Weeks in Select Treatment-Naïve, Non-Cirrhotic GT 1b Chinese Patients

Pilot, open-label study to evaluate 3 week response guided triple therapy in non-cirrhotic Chinese patients with GT 1b HCV who have RVR.



- 3 patients with RVR at Day 2 and 3 weeks of DAA achieved SVR12
- No D/C or significant AEs

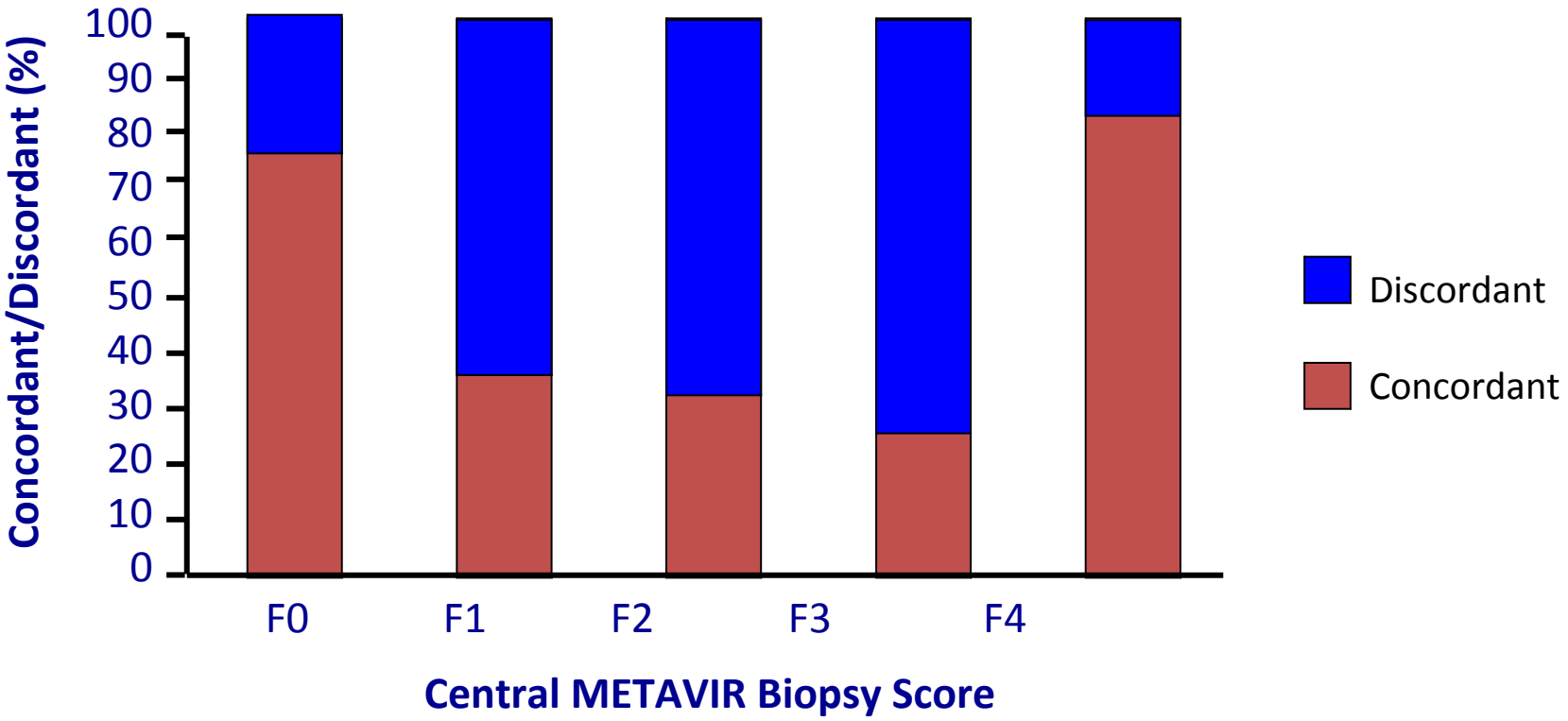
RVR=plasma HCV RNA <500 IU/ml by Day 2

Lau, AASLD, 2015, LB-23

Why should I treat my patients with mild hepatitis C?

- Disease staging is not faultless

Proportion of concordant and discordant liver biopsy (N = 234) staging between 3 pathologists



Diagnostic Value for Fibrosis
(F234 vs F0F1) Right Lobe vs Left Lobe Biopsy (N = 124)

- Discordance rate = 33%
- Kappa = 0.50
- AUROC = 0.76

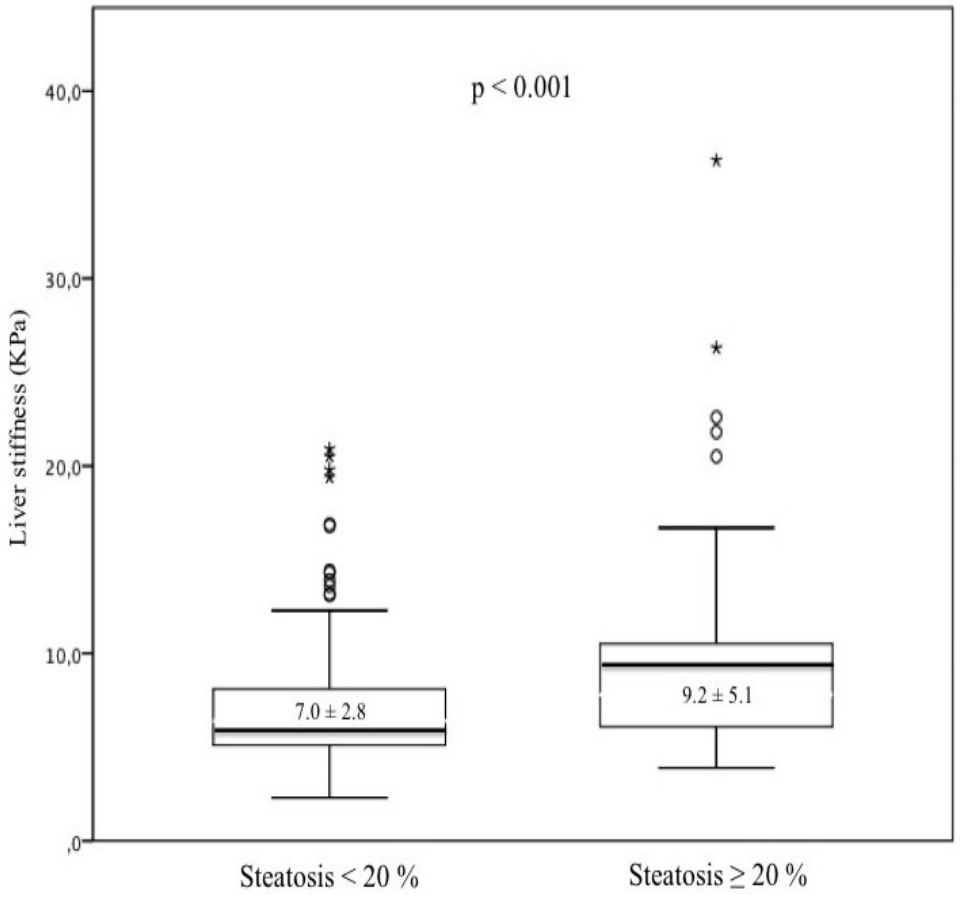
Regev A, et al. Am J Gastroenterol. 2002;97:2614-2618.

Metaanalysis of Transient Elastography

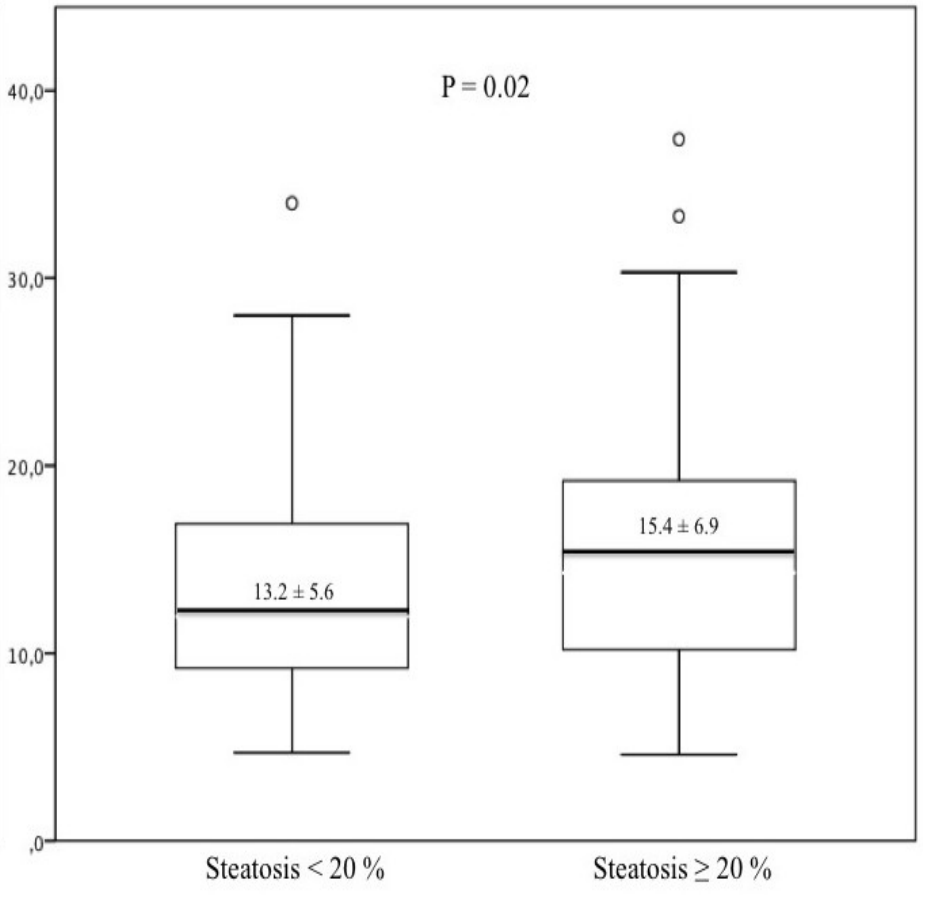
	Number of Studies	Nr. of patients	AUROC			Cut-off (kPa)		
			≥ F2	≥ F3	F4	≥ F2	≥ F3	F4
Talwalkar et al	9	2.083	0,870	N/A	0,957	N/A	N/A	N/A
Stebbing et al.	22	4.760	0,84	0,89	0,94	7,81	N/A	15,56
Friedrich-Rust et al.	50	8.206	0,84	0,89	0,94	7,65	N/A	13,01
Tsochatzis et al.	40	7.723	N/A	N/A	N/A	7,3	10,2	15,0

Chon et al. PlosOne *2012*

Steatosis affects the performance of liver stiffness measurement for fibrosis assessment in patients with genotype 1 chronic hepatitis C



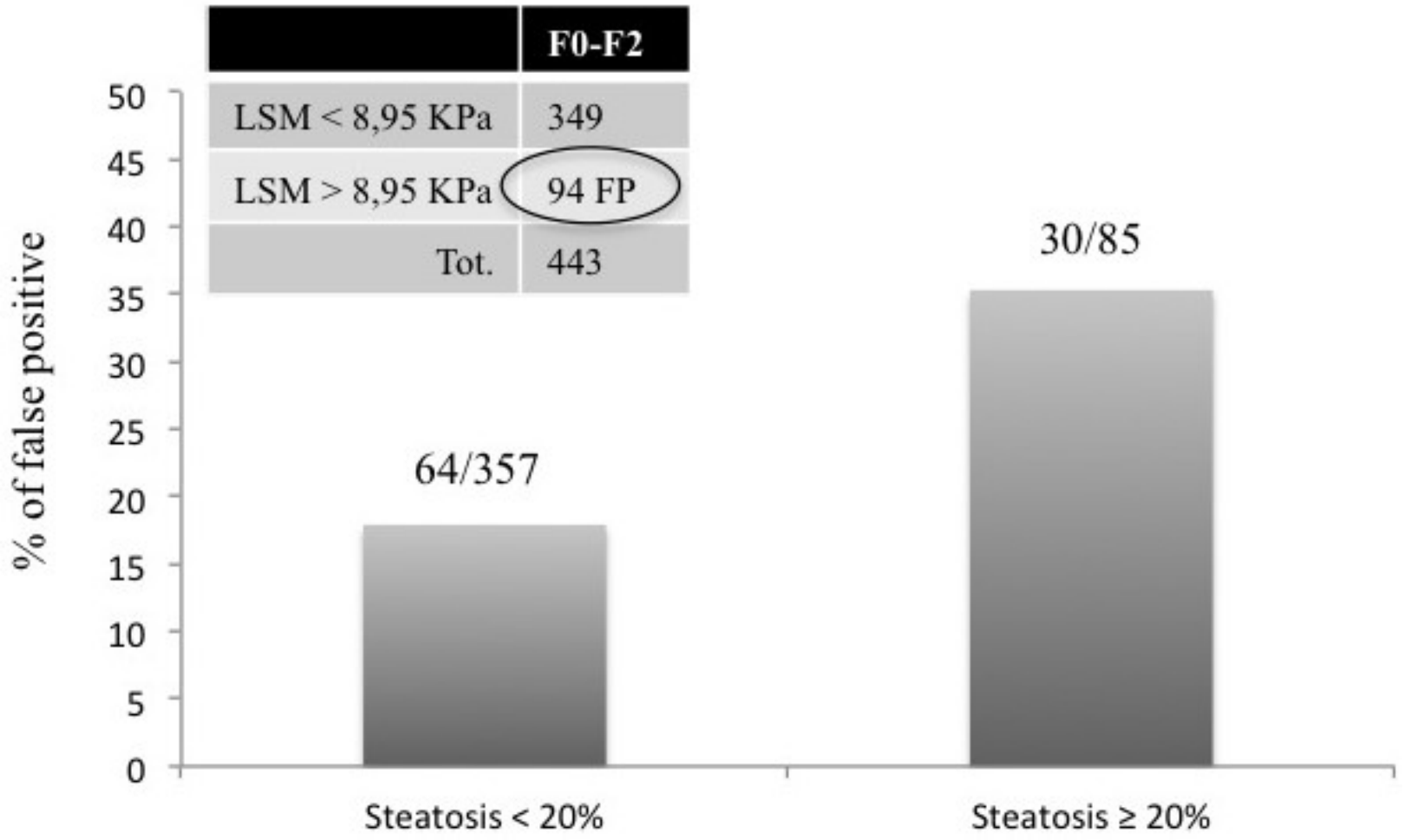
F0-F2



F3-F4

Macaluso FS et al. J Hepatol. 2014;61:523-9.

Steatosis affects the performance of liver stiffness measurement for fibrosis assessment in patients with genotype 1 chronic hepatitis C

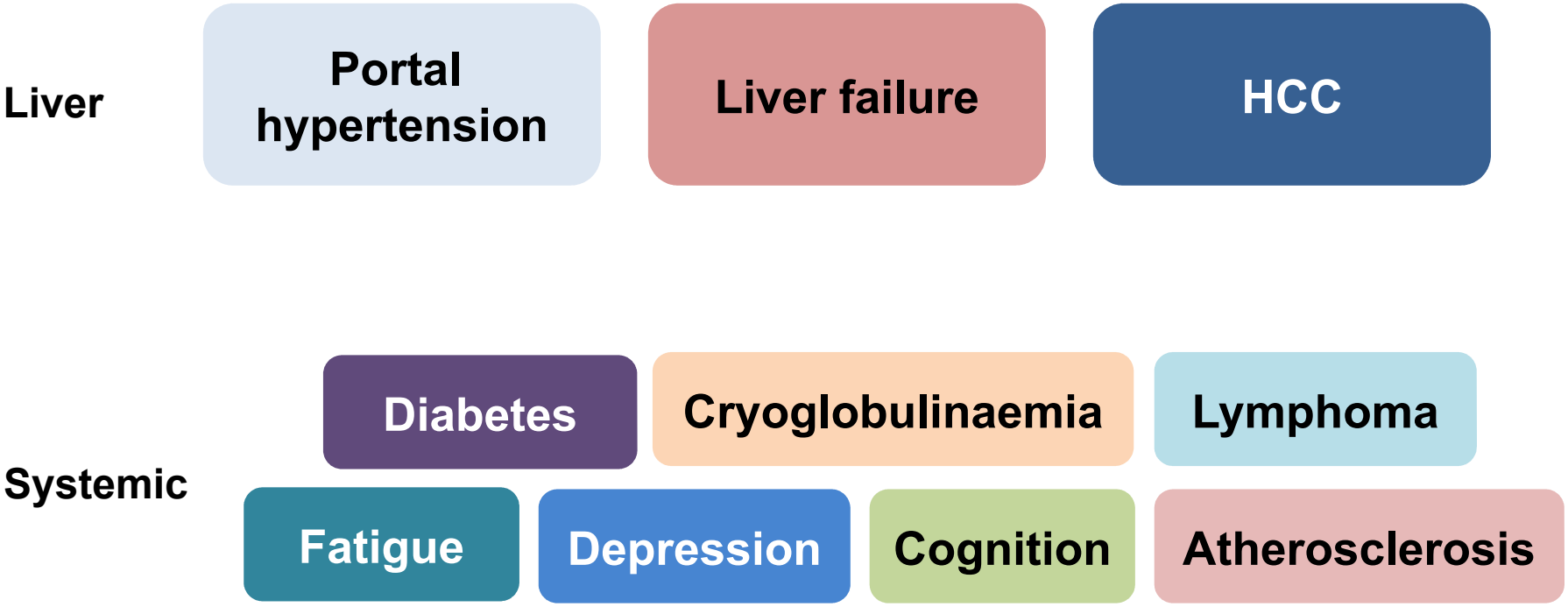


Macaluso FS et al. J Hepatol. 2014;61:523-9.

Why should I treat my patients with mild hepatitis C?

- HCV causes significant extra-hepatic morbidity

Hepatitis C: beyond the liver….



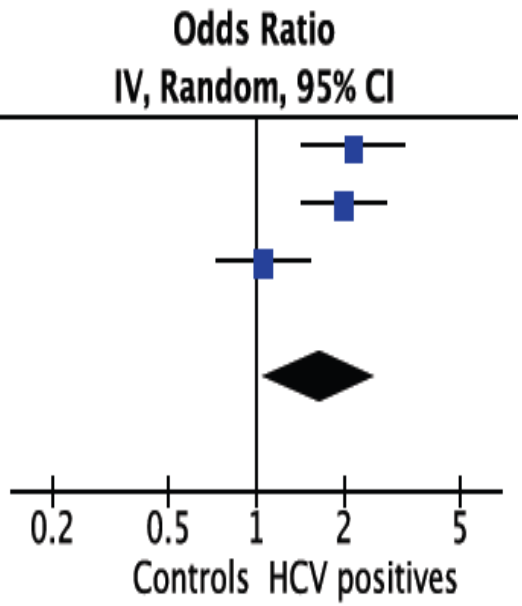
Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic Morbidity and Mortality of Chronic Hepatitis C. Gastroenterology. 2015;149:1345-60

HCV infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies

Study or Subgroup	HCV Events	HCV Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Guiltinan 2008	73	10259	34	10259	31.8%	2.16 [1.43, 3.24]	2008
Lee 2012	38	760	477	18541	34.8%	1.99 [1.42, 2.80]	2012
Vajdic 2015	59	14498	54	14048	33.4%	1.06 [0.73, 1.53]	2015
Total (95% CI)		**25517**		**42848**	**100.0%**	**1.65 [1.07, 2.56]**	
Total events	170		565				

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 8.37$, df = 2 (P = 0.02); $I^2 = 76\%$

Test for overall effect: Z = 2.25 (P = 0.02)



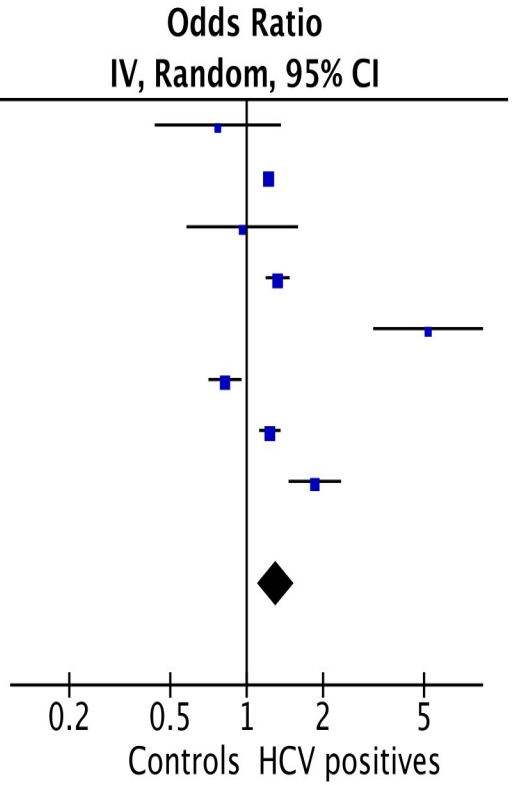
Petta S, et al. Gastroenterology. 2016;150:145-155

HCV infection is associated with increased cerebro-cardiovascular events: a meta-analysis of observational studies

Study or Subgroup	HCV Events	HCV Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Arcari 2006	23	52	269	530	5.9%	0.77 [0.43, 1.36]	2006
Butt 2009	6169	82083	5594	89582	17.8%	1.22 [1.18, 1.27]	2009
Forde 2012	16	4809	248	71668	6.9%	0.96 [0.58, 1.60]	2012
Liao 2012	482	4094	1499	16376	16.7%	1.32 [1.19, 1.48]	2012
Adinolfi 2013	33	79	90	741	7.0%	5.19 [3.15, 8.54]	2013
Hsu CS 2013	220	2875	1141	12452	15.7%	0.82 [0.71, 0.95]	2013
Enger 2014	584	21919	1456	67109	16.9%	1.23 [1.12, 1.36]	2014
Pothineni 2014	84	1434	480	14799	13.2%	1.86 [1.46, 2.36]	2014
Total (95% CI)		**117345**		**273257**	**100.0%**	**1.30 [1.10, 1.55]**	
Total events	7611		10777				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 76.44$, df = 7 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: Z = 3.08 (P = 0.002)



High Heterogeneity!!!!!!

Petta S, et al. Gastroenterology. 2016;150:145-155

Association Between Antiviral Treatment and Extrahepatic Outcomes in Patients with HCV

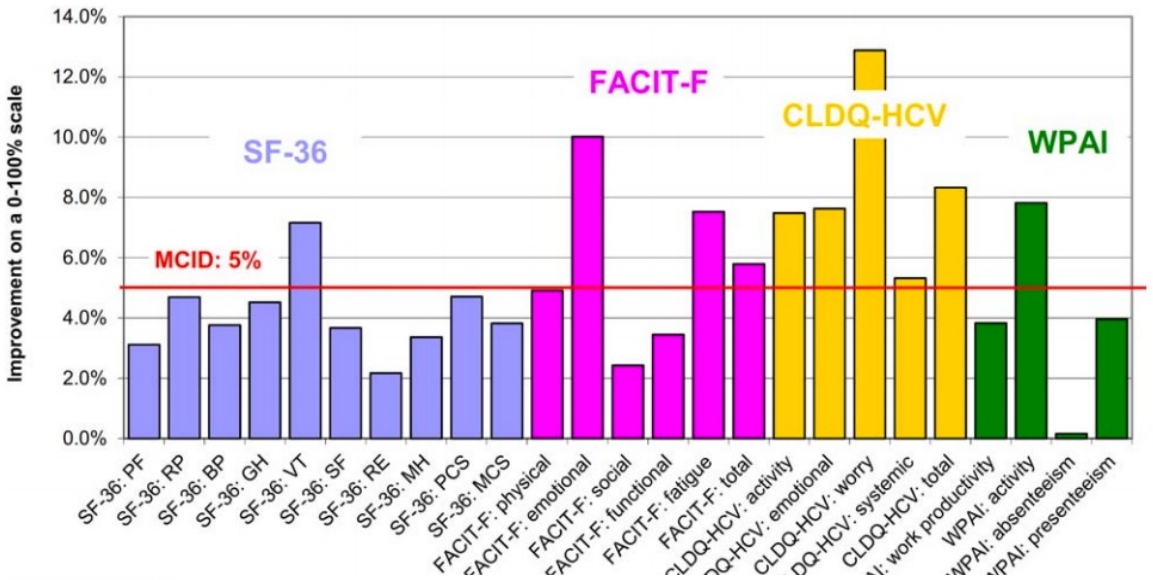
Propensity score study in Taiwan: 12,384 eligible to IFN/RBV vs 24,768

Cumulative 8-yr incidence in treated vs not treated

End stage renal disease	**0.15% vs 1.32%**	***HR 0.15 (95% CI 0.07-0.31)***
Acute coronary syndrome	**2.21% vs 2.96%**	***HR 0.77 (95% CI 0.62-0.97)***
Ischemic stroke	**1.31% vs 1.76%**	***HR 0.62 (95% CI 0.46-0.83)***
Autoimmune catastrophes	**0.57% vs 0.48%**	***P<0.816***

Hsu et al, Gut 2015;64:495-503

Post-SVR12 improvements in PRO scores
Results From the ION-1,-2, and -3 Clinical Trials



1,952 pts treated for
8 (431)
12 (867)
24 wks (654)

LDV/SOF (1,080)
LDV/SOF/RBV (872).

FACIT-F total: post-treatment week 12

Enrolled in the USA	10.680 ±1.566	<0.0001
Baseline anxiety	-7.015 ±1.518	<0.0001
Baseline depression	-12.113 ±1.373	<0.0001
Baseline fatigue	-7.237 ±1.684	<0.0001
Baseline insomnia	-5.032 ±1.464	0.0006
Baseline type 2 diabetes	-6.241 ±1.781	0.0005

The most consistent predictors of lower PRO scores at all time points (**P<**0.001).

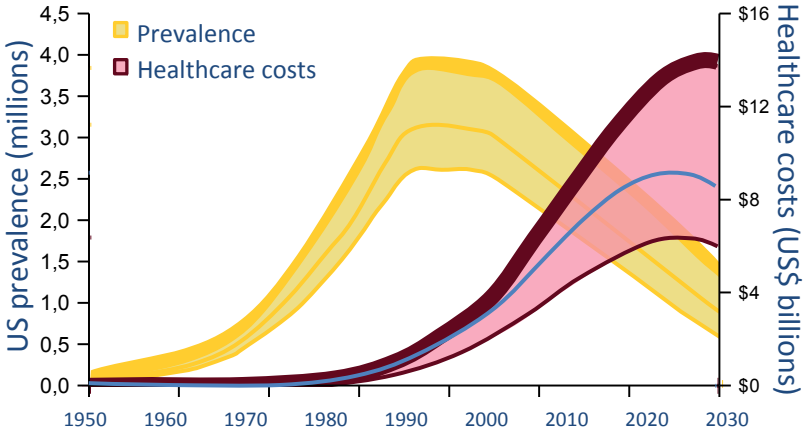
Younossi Z et al. HEPATOLOGY 2015; 61: 1798-1808

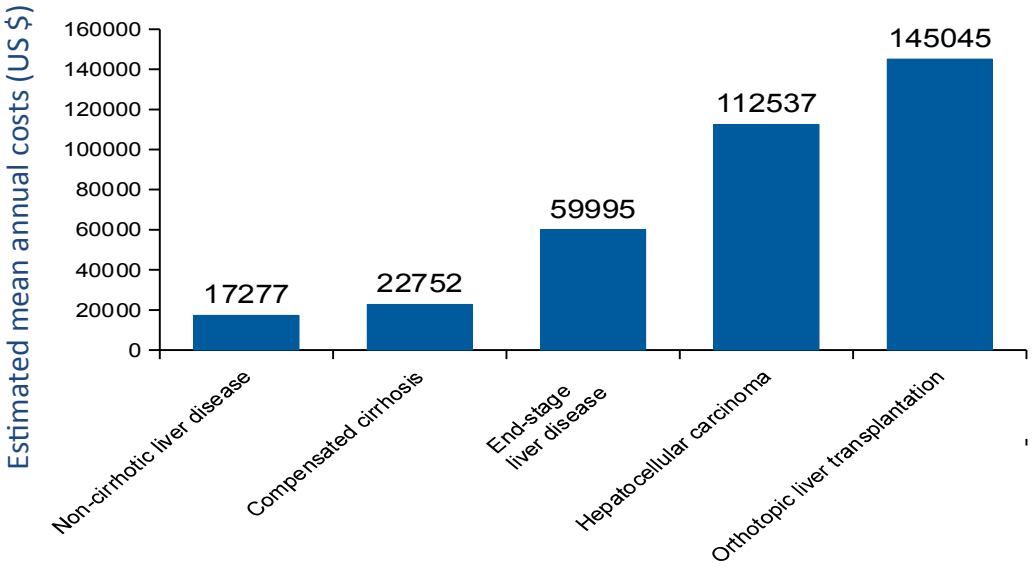
Why should I treat my patients with mild hepatitis C?

- Best cost-effectiveness is obtained treating at an early stage of disease

Management of HCV-related liver disease is costly

Costs associated with the care of HCV-infected patients increase with disease severity

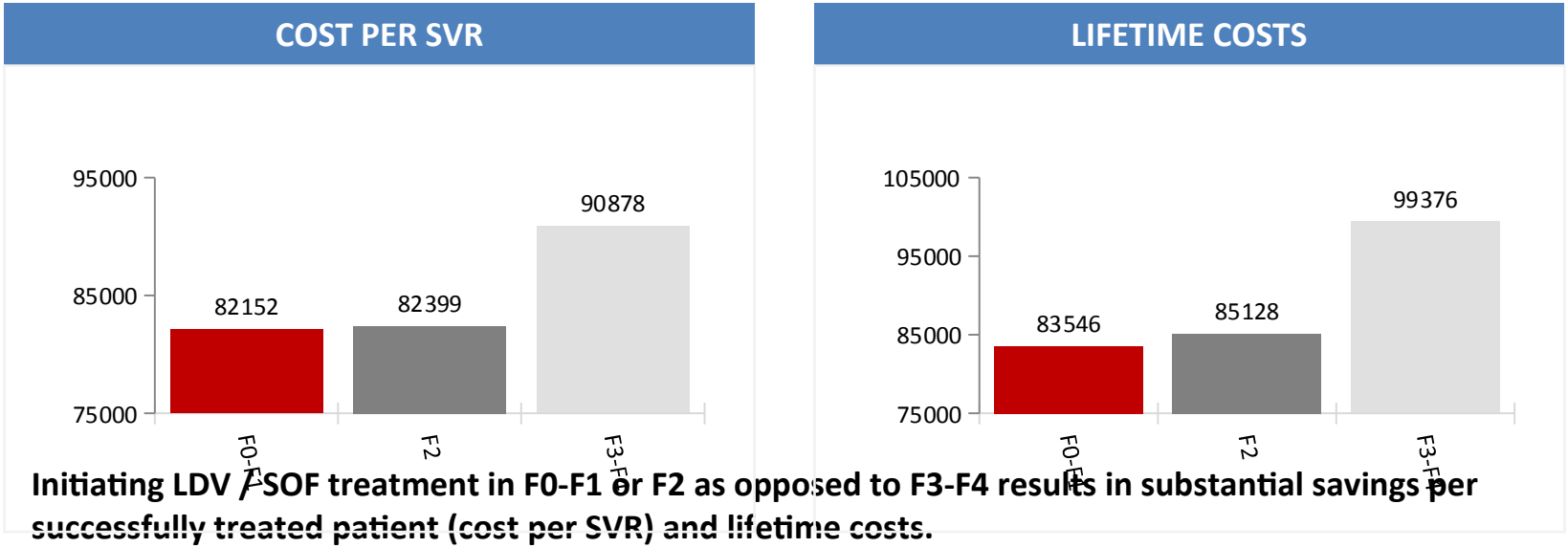




Razavi H, et al. Hepatology 2013;57:2164–70; Gordon SC, et al. Hepatology 2012;56:1651–60.

Evaluation of Health Outcomes from LDV/SOF Treatment of Patients with Early vs. Advanced Liver Fibrosis

Initiating LDV/SOF treatment at F0-F1 and F2 rather than F3-F4 reduces lifetime costs of treatment, and has a lower cost per SVR



Initiating LDV / SOF treatment in F0-F1 or F2 as opposed to F3-F4 results in substantial savings per successfully treated patient (cost per SVR) and lifetime costs.

Ahmed A, AASLD, 2014, #1751

Benefits of early vs delayed treatment

- Retrospective analysis of pts with HCV infection in VA Clinical Case Registry[1]
  - Early vs delayed treatment associated with reduced risk of liver-related events and death
  - Risk of delaying treatment increases as disease severity increases, due to diminished likelihood of achieving SVR
- Markov disease utility state-transition modeling of OBV/PTV/RTV + DSV ± RBV therapy in genotype 1 HCV infection[2]
  - Treatment prolongs survival and quality of life vs watchful waiting
  - Treatment-related survival benefits of previously treated pts 1% to 6% lower than treatment-naive pts

1. McCombs J, et al. EASL 2015. Abstract O003. 2. Johnson S, et al. EASL 2015. Abstract P0806.

And the true question is ……

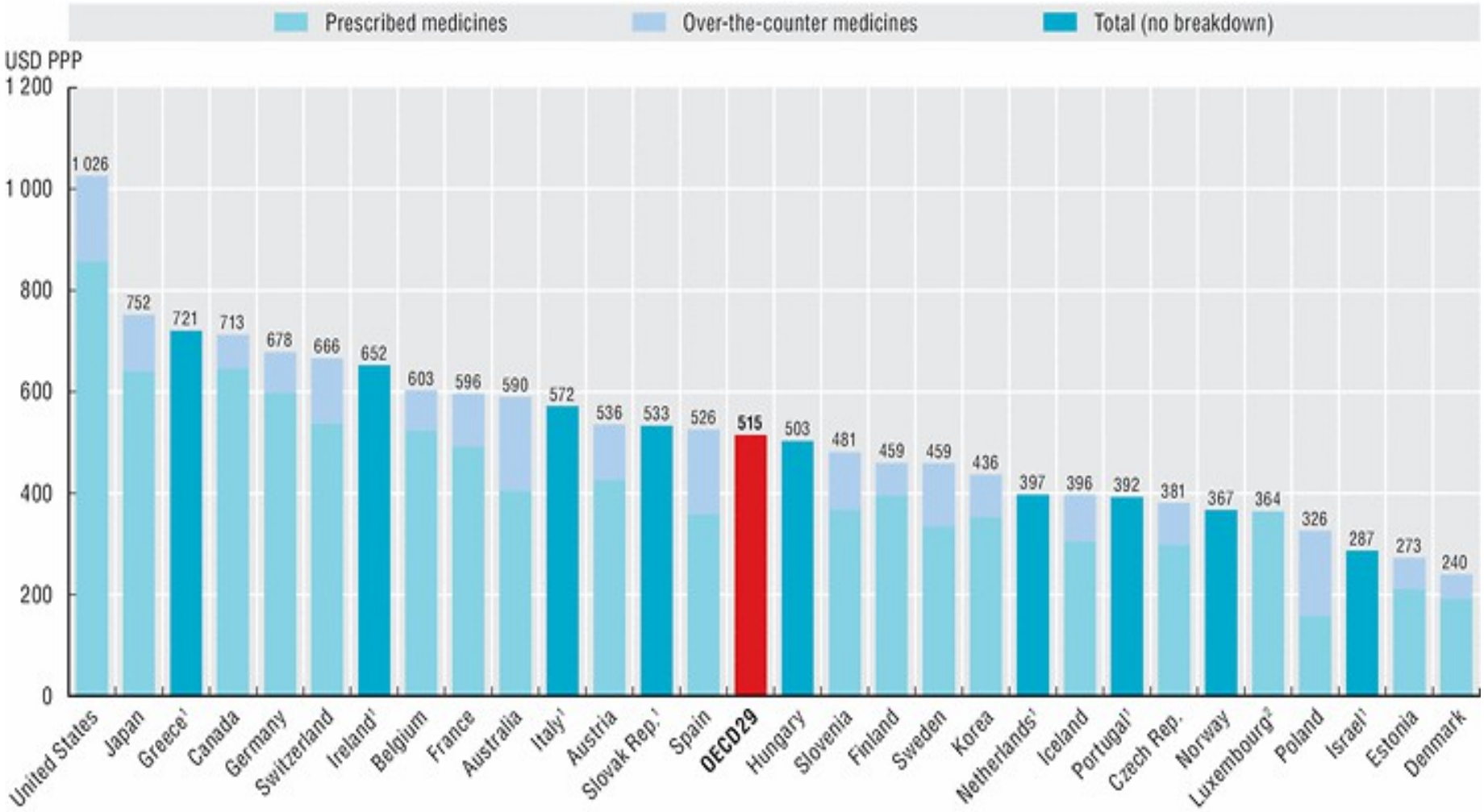
Am I allowed to treat my patients with mild hepatitis C?

Reimbursement of DAAs across some EU countries

	Ombitasvir/Dasabuvir/ Paritaprevir	Sofosbuvir/ Ledipasvir	Sofosbuvir	Simeprevir	Daclatasvir	Source
	Reimbursement (fibrosis stages)	**Reimbursement (fibrosis stages)**	**Reimbursement (fibrosis stages)**	**Reimbursement (fibrosis stages)**	**Reimbursement (fibrosis stages)**	
Germany	F0-F4	Per label	Per label	Per label	Per label	Lauer Taxe (http://www.ifaffm.de/de/ifa-fuer-anbieter/ifa-redaktionskalender.html). Official web site. Protected by password
France	F3-F4 + F2 severe	F4-F3, F2 severe	F4-F3, F2 severe	F4-F3, F2 severe	F4-F3, F2 severe	Official Journal, JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE, aout 2015
UK	F4 (NHS policy) Scotland: F0-F4	See NHS policy	NICE approved (+PegR)	See NHS policy	See NHS policy	http://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/06/hep-c-cirrhosis-polcy-statmnt-0615.pdf
Italy	F3-F4	F3-F4	F3-F4	F0-F4	F3-F4	GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA No. 118, 2015
SPAIN	F2-F4	Per label	F4 + severe	Per label	Per label	Prices and reimbursement on https://botplusweb.portalfarma.com/botplus.aspx (protected by password)
Sweden	F2-F4	F3-F4	F3-F4	F3-F4	F3-F4	www.apoteket.se or www.apotekhjartat.se. www.TLV.se
Finland	F3-F4	F3-F4	F3-F4	F3-F4	F3-F4	https://easiointi.kela.fi/laakekys_app/LaakekysApplication?kieli=en
DENMARK	F3-F4	F3-F4 (RADS Guid.)	F3-F4 (RADS Guid.)	F3-F4 (RADS Guid.)	F3-F4 (RADS Guid.)	prices and reimburseemnt status on http://www.medicinpriser.dk/
AUSTRIA	F2-F4	F2-F4	F2-F4	Not reimbursed	F2-F4	http://www.hauptverband.at/portal27/portal/hvbportal/emed/
Portugal	NA	All Fs	All Fs	Not reimbursed	Not reimbursed	www.infarmed.pt
Turkey	NA	Not reimbursed	Not reimbursed	Not registered	Not registered	
Israel	F3-F4	Not reimbursed	Not reimbursed	Not reimbursed	Not reimbursed	http://www.old.health.gov.il/units/pharmacy/trufot/Ycran_ListN.asp?Letter=viekirax&Sr_Type=T_Name&p=1&safa=e
Switzerland	F2-F4	F3-F4	F3-F4	F3-F4	--	Compendium.ch
Luxembourg	F0-F4	Per label	Per label	Per label	Per label	http://www.cns.lu/prestataires/?m=55-41-28&p=248
Netherlands	F0-F4	F0-F4	F3/F4 only	Full label	GT1 and GT4	Prices and reimbursement on https://www.medicijnkosten.nl/

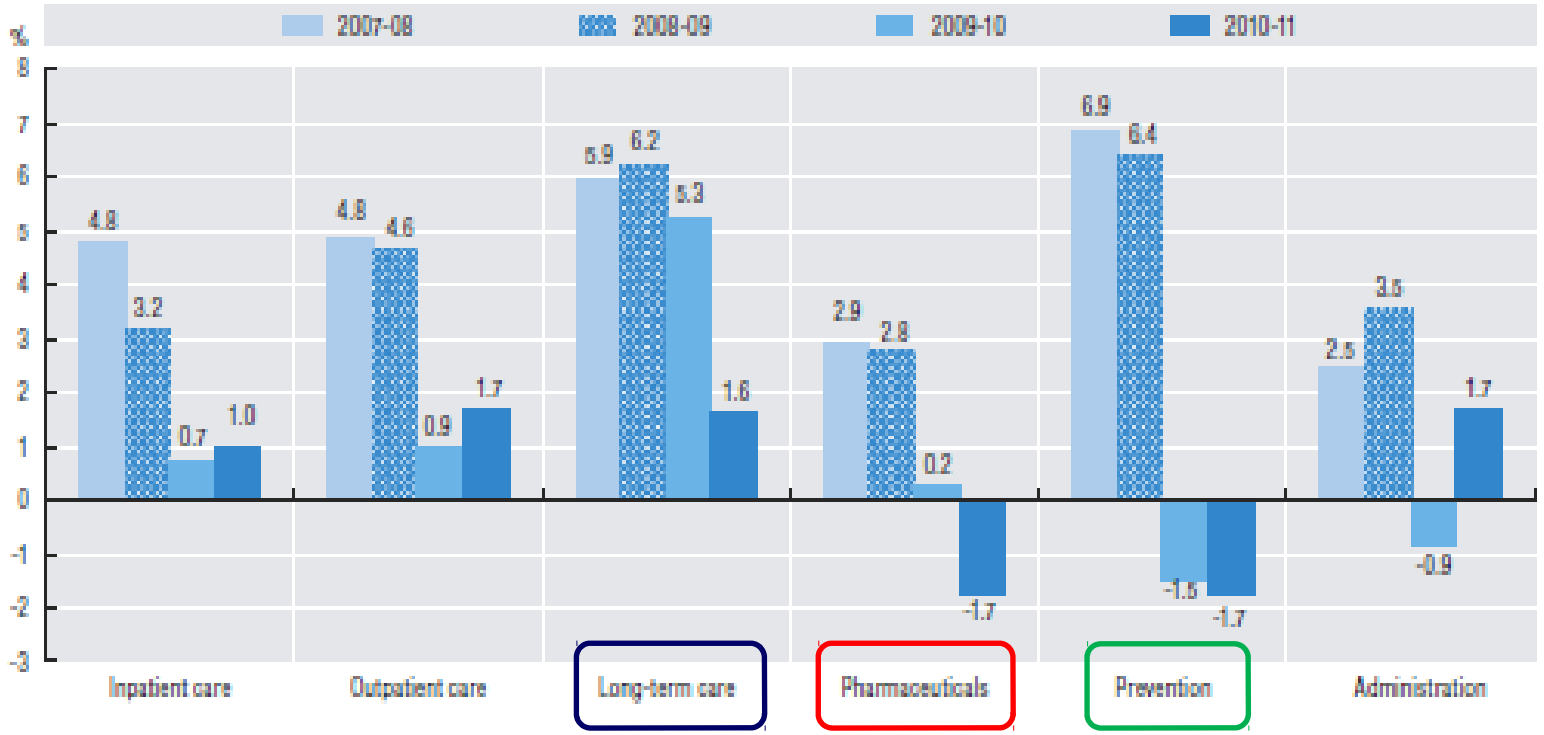
Pharmaceutical Expenditure per Capita

OECD Health Statistics 2015



Growth Change for Selected Functions

van Gool, *et al.*, OECD Working Papers 2014; DOI: 10.1787/18152015



- Average annual growth change for selected functions 2000-2011