16th Residential Course on Clinical Pharmacology of Antiretrovirals

HCV Treatment of Patients with Compensated Cirrhosis

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One and Two-year Survival Rate in Studies Including only Compensated or Decompensated Patients

- Treatment indication and timing is complex and should take into account LT availability

- Treatment recommendations are limited in terms of possible DAA combinations

- Follow-up is complex

D'Amico G et al, J Hepatol 2006;44:217-231

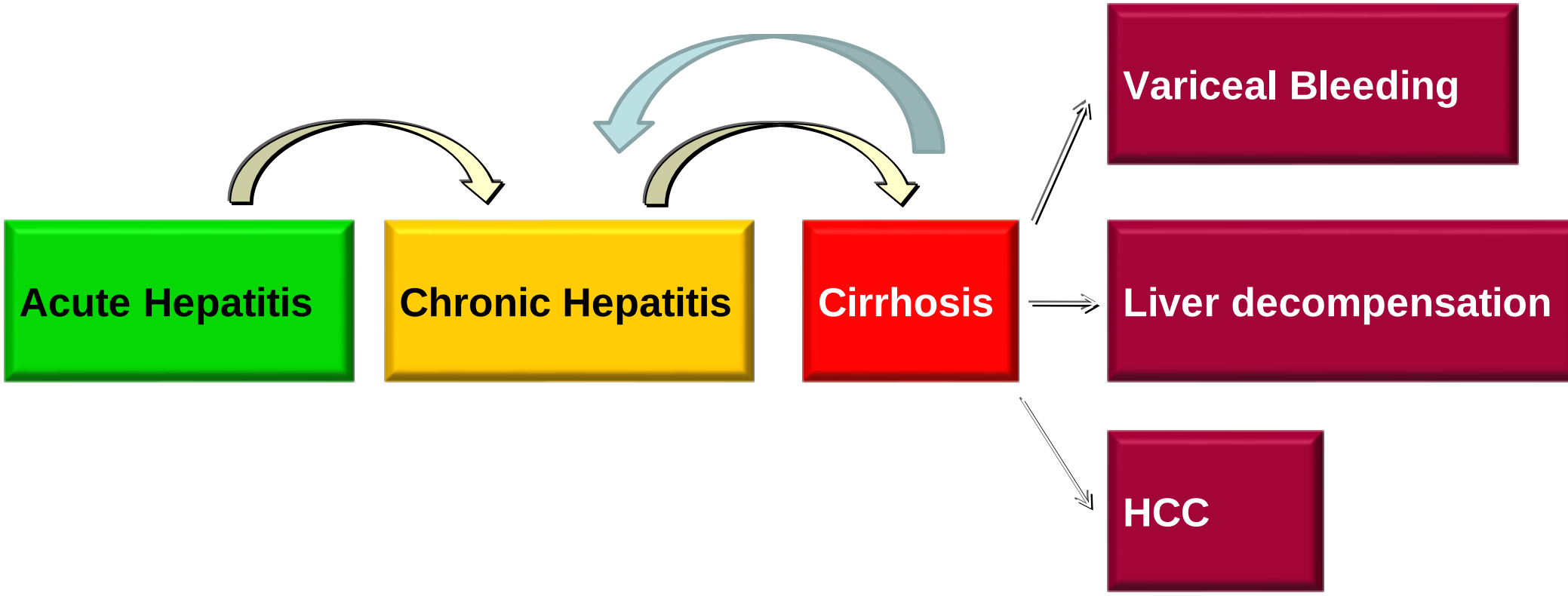
Treatment of HCV Patients with Cirrhosis: Outline

- Indication to Treatment (Who to Treat?)
- Treatment recommendations (How to Treat?)
- Post Treatment Fup and Management

The Endpoint of Treatment in HCV: SVR

- To cure HCV infection, in order to:
  - Prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC and death
  - Improve quality of life and remove stigma
  - Prevent onward transmission of HCV

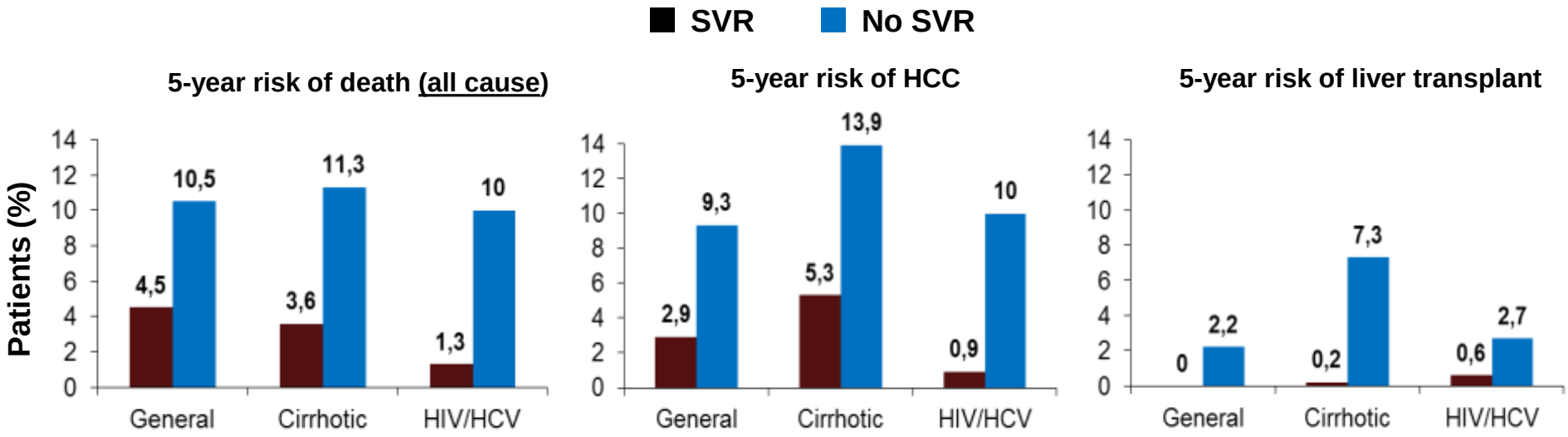
Natural History of Hepatitis C



Modified by Lauer and Walker NEJM 2001;345:41-52

SVR is Associated with a Reduced Mortality, HCC and Liver Transplant

Systematic review of 129 studies of IFN-based therapy in 34,563 HCV patients



Achieving SVR was associated with:

62–84% reduction in all-cause mortality

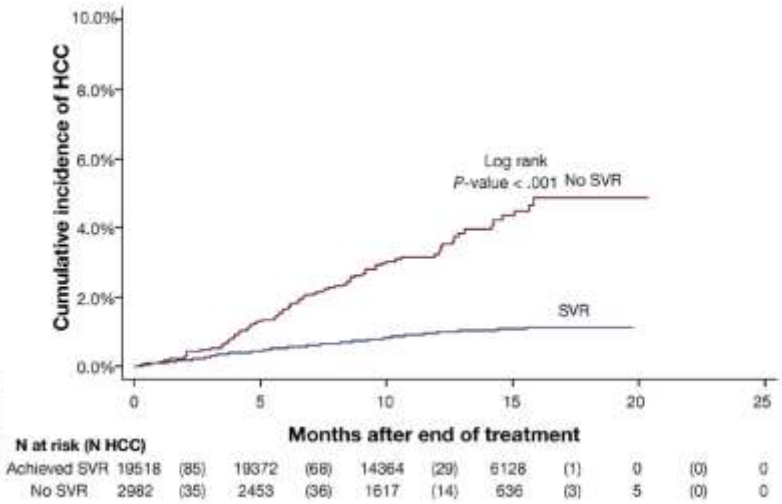
68–79% reduction in risk of HCC

90% reduction in risk of liver transplant

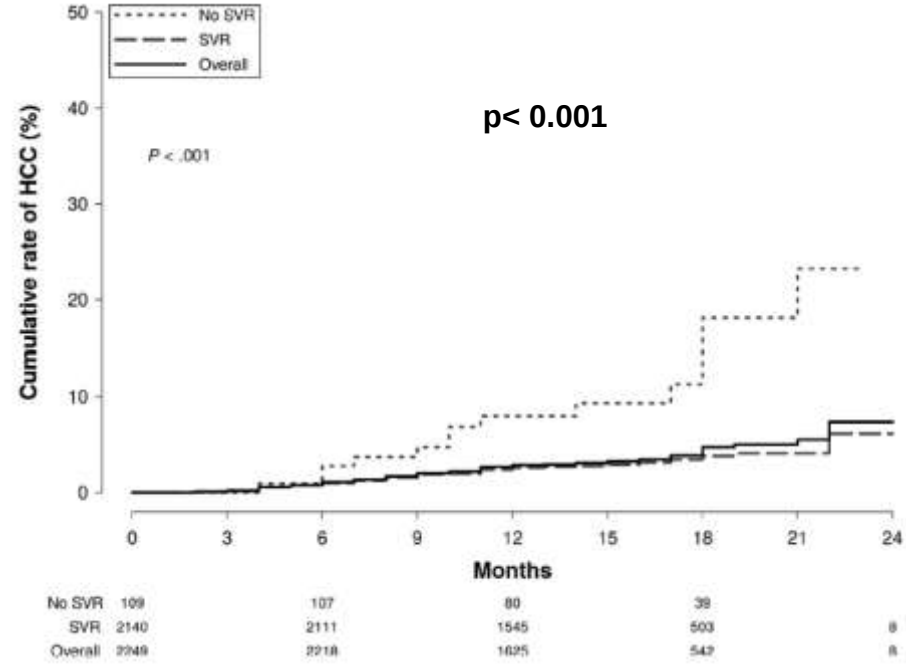
Saleem J, et al. Hepatology 2014

DAAs-SVR reduces HCC occurrence in cirrhotic patients

Compared to patients without SVR, those with SVR had a significantly reduced risk of HCC (76% risk reduction)



Kanwal F et al. Gastroenterology 2017



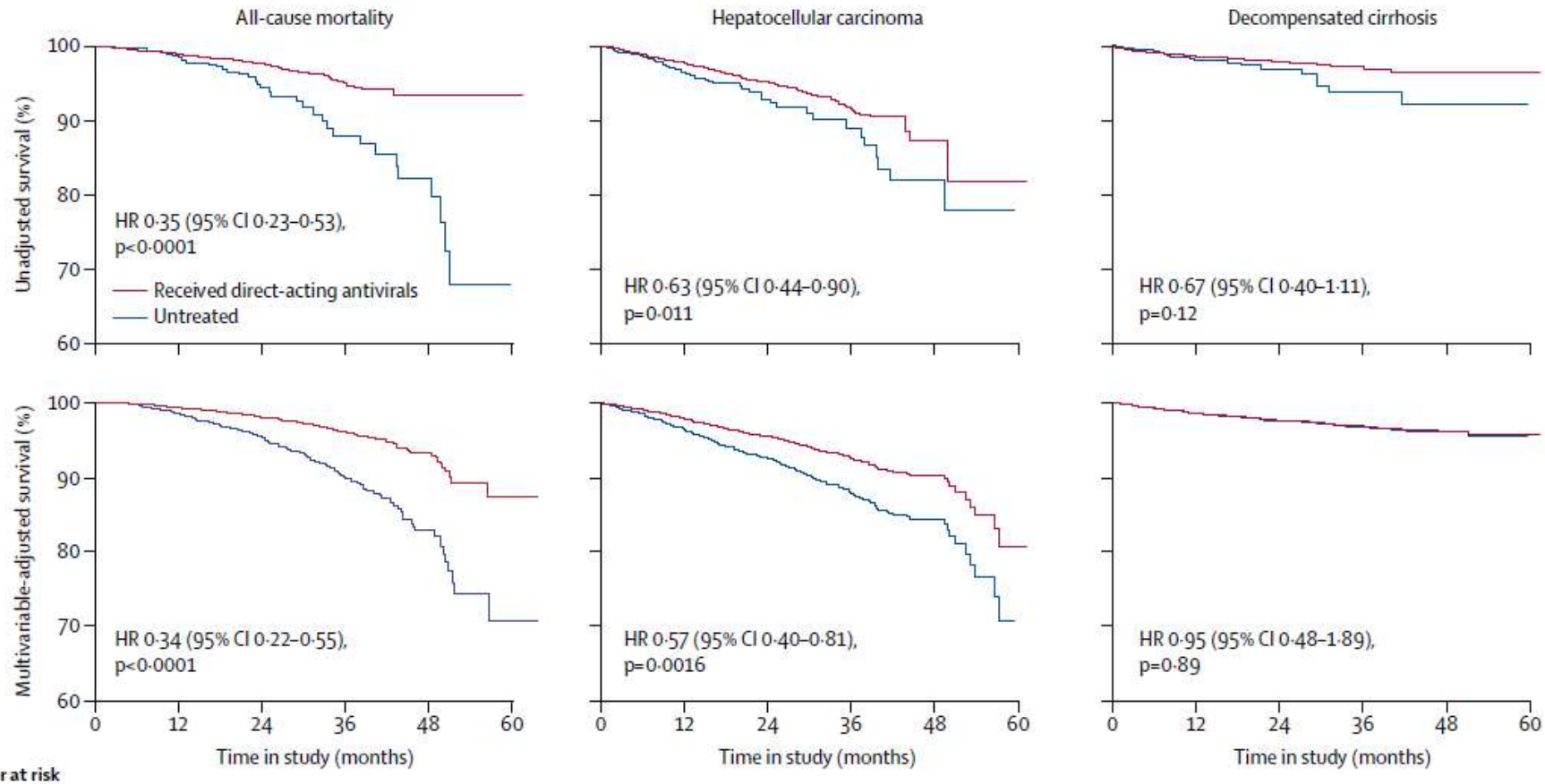
p< 0.001

Calvaruso et al. Gastroenterology 2018

Results confirmed by other studies:

Romano A. et al. J Hepatol. 2018 NAVIGATORE STUDY.
Renzulli M. et al. Eur Radiol. 2018.
Ioannou GN et al. J Hepatol. 2017.
Ogata F at al. Oncology 2017.
Backus LI et al. Hepatology. 2017.

DAA Treatment Improves Survival in HCV Cirhosis

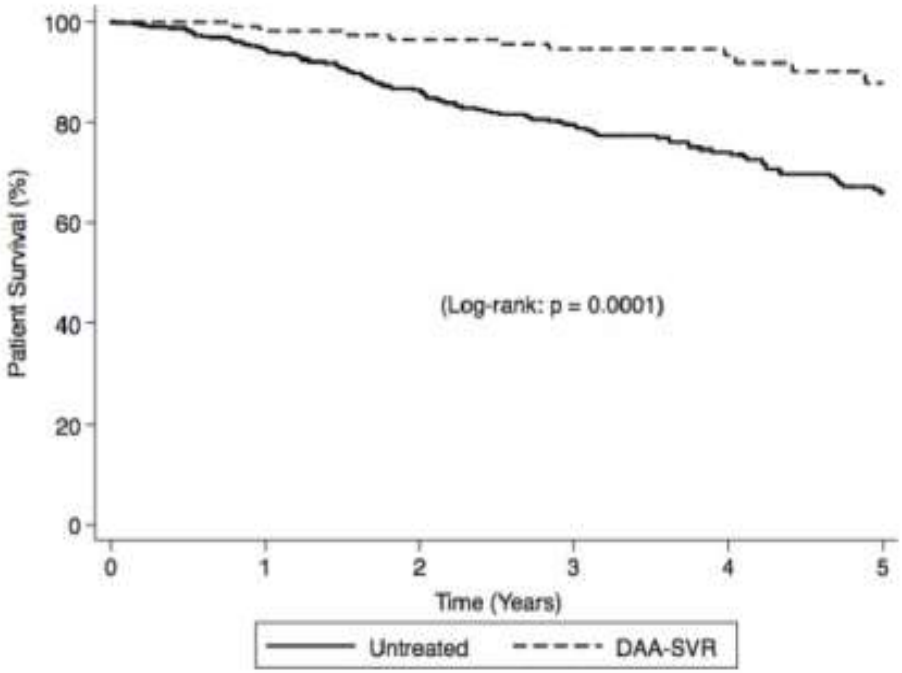


Number at risk (number censored)																		
Received direct-acting antivirals	2823	2457	1803	610	25	2	2795	2389	1715	575	23	2	2810	2419	1768	596	25	2
	(0)	(338)	(963)	(2125)	(2704)	(2727)	(0)	(347)	(964)	(2065)	(2607)	(2627)	(0)	(353)	(987)	(2150)	(2718)	(2741)
Untreated	3045	560	186	82	37	0	3045	543	178	76	33	0	3045	552	185	81	37	0
	(0)	(2474)	(2834)	(2930)	(2971)	(3004)	(0)	(2468)	(2821)	(2918)	(2956)	(2988)	(0)	(2474)	(2837)	(2937)	(2980)	(3017)

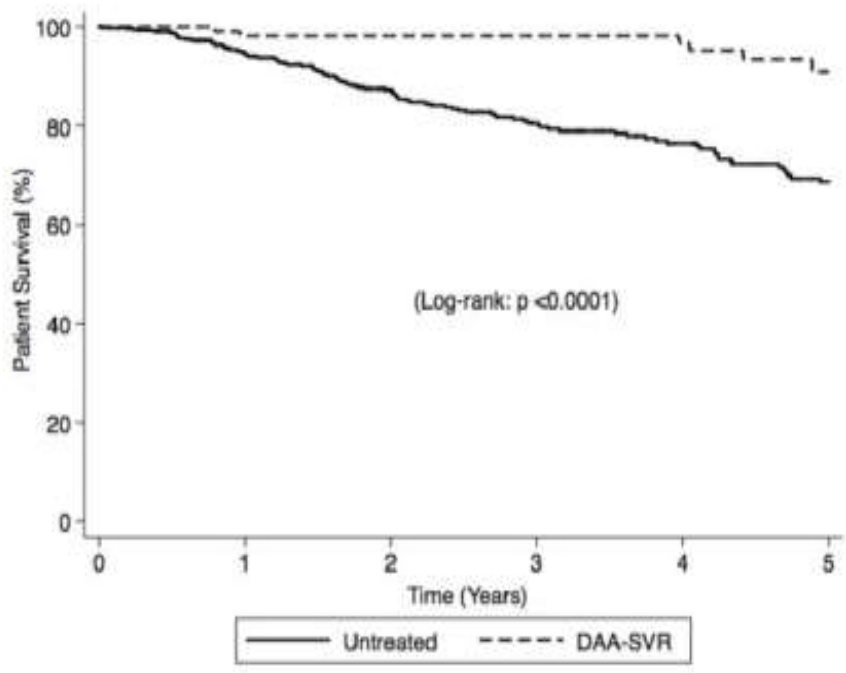
Carrat et al, Lancet 2019

Improved Survival of HCV Patients with HCC Who Received DAAs

Overall Mortality



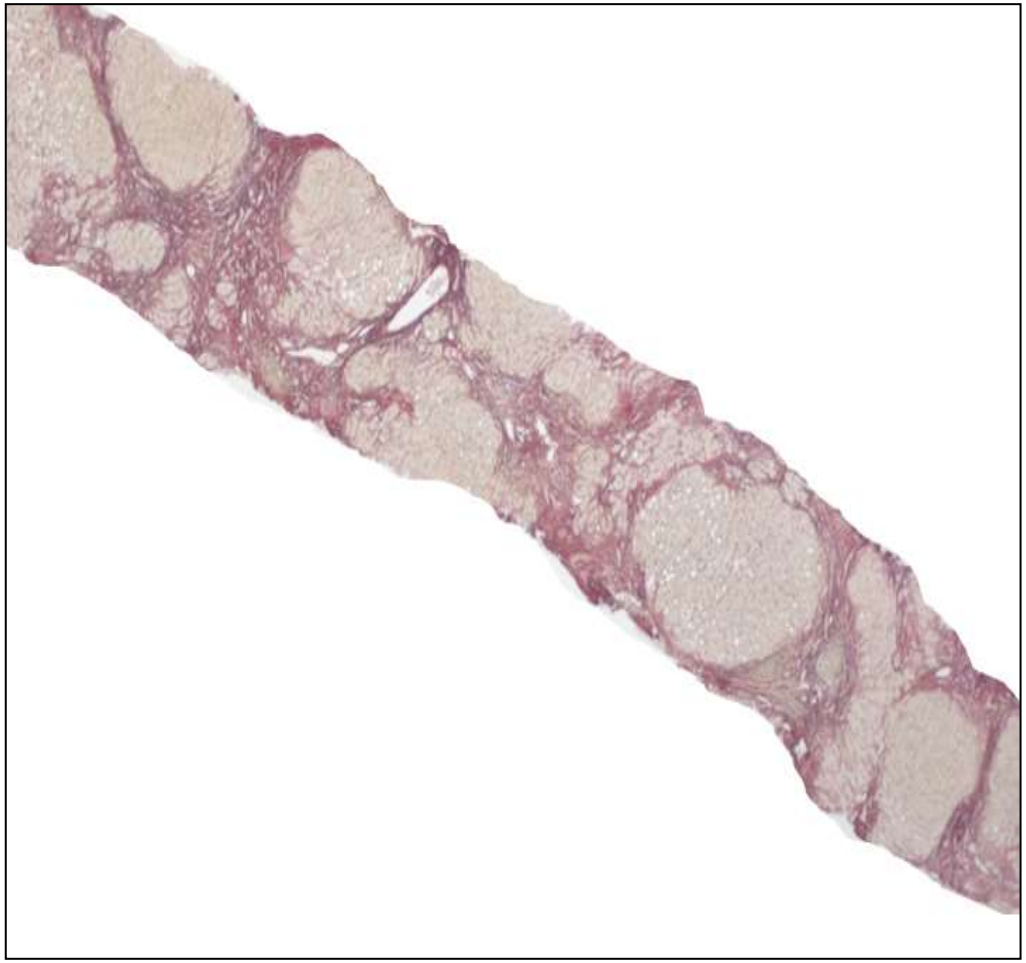
Liver related Mortality



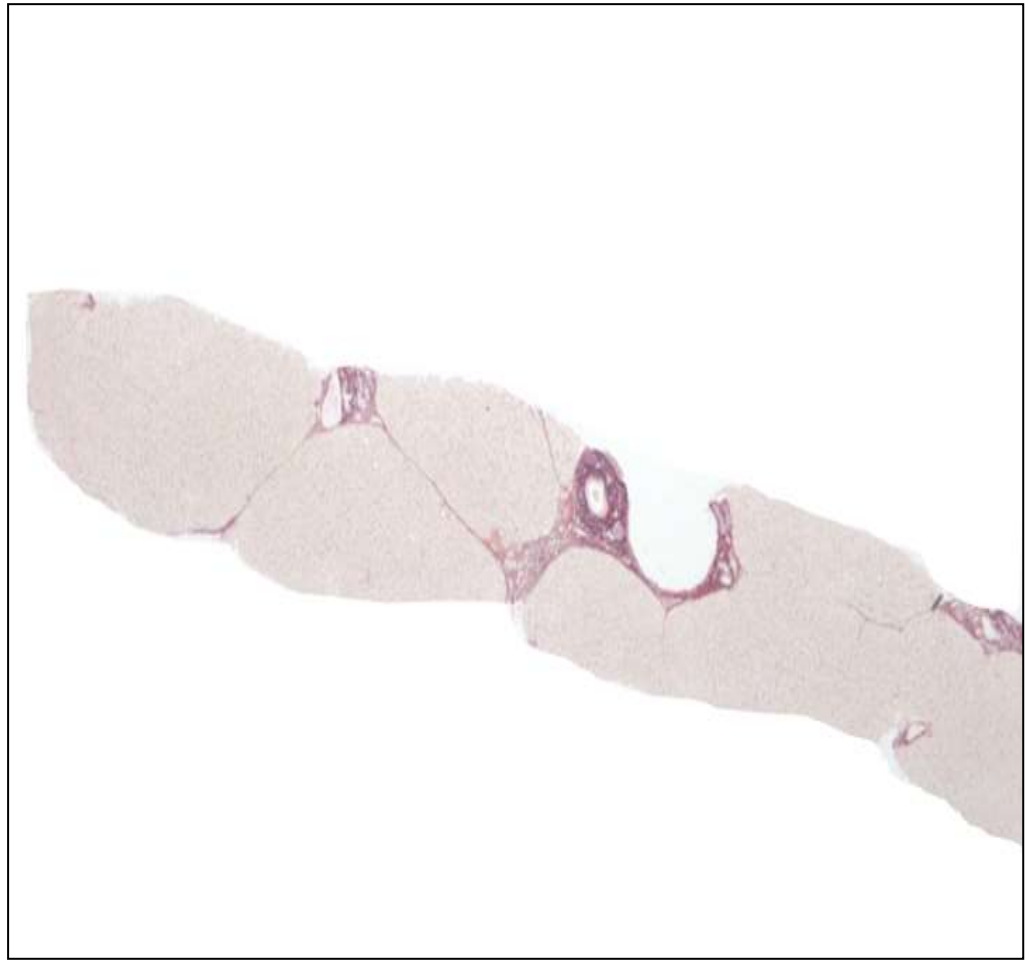
Dang S et al, Hepatology 2020

Cirrhosis Regression in HCV Pts Following an SVR: a Myth no More

Pre-TX

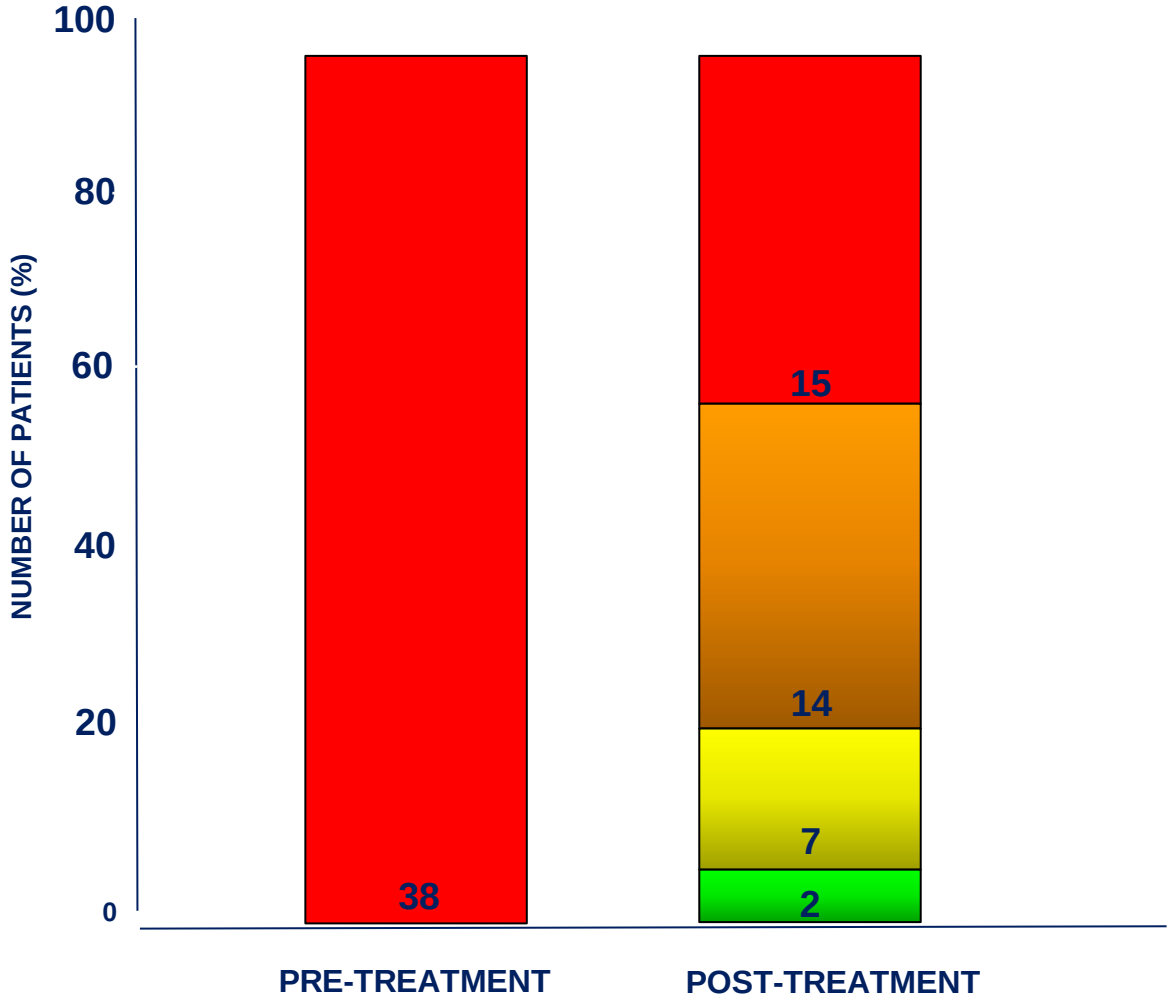


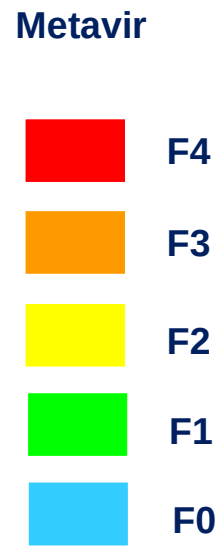
5 years post-SVR



D'Ambrosio R et al Hepatology 2012, 56(2):532-43

Rates of Cirrhosis Regression According to the METAVIR Scoring System





Cirrhosis Regression in 23 (61%) Patients

D'Ambrosio R et al Hepatology 2012, 56(2):532-43

Treatment of HCV Patients with Cirrhosis: Outline

- Indication to Treatment (Who to Treat?)
- Treatment recommendations (How to Treat?)
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Combining DAAs to Maximize Efficacy

NS5B Polymerase Inhibitor

NS5A Inhibitors

Protease Inhibitors

Sofosbuvir + **Velpatasvir (NS5A)**

Grazoprevir (PI)
Glecaprevir (PI)
+
Elbasvir (NS5A)
Pibrentasvir (NS5A)

Sofosbuvir + **Velpatasvir (NS5A)** + **Voxilaprevir (PI)**

Pan-genotypic DAAs Are the Core of The EASL 2020 CPG

Type of treatment	Genotype	Cirrhosis status	Prior treatment experience	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir	Sofosbuvir/ velpatasvir/ voxilaprevir	Grazoprevir/ elbasvir
Genotype/subtype determination-based treatment	Genotype 1a, 1b, 2, 4, 5 and 6	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	12 weeks (genotype 1b only)
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve		12 weeks		
			Treatment-experienced				
	Genotype 3	No cirrhosis	Treatment-naïve	12 weeks	8 weeks	No	No
			Treatment-experienced		12 weeks		No
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve	12 weeks with weight-based ribavirin[a]	8-12 weeks[b]	12 weeks[a]	No
			Treatment-experienced		16 weeks		No
	Subtype 1l, 4r, 3b, 3g, 6u, 6v or any other subtype naturally harbouring one or several NS5A RASs[c]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 weeks	No
			Treatment-experienced				
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

Easl 2020 HCV Treatment Recommendations, J Hepatol in press

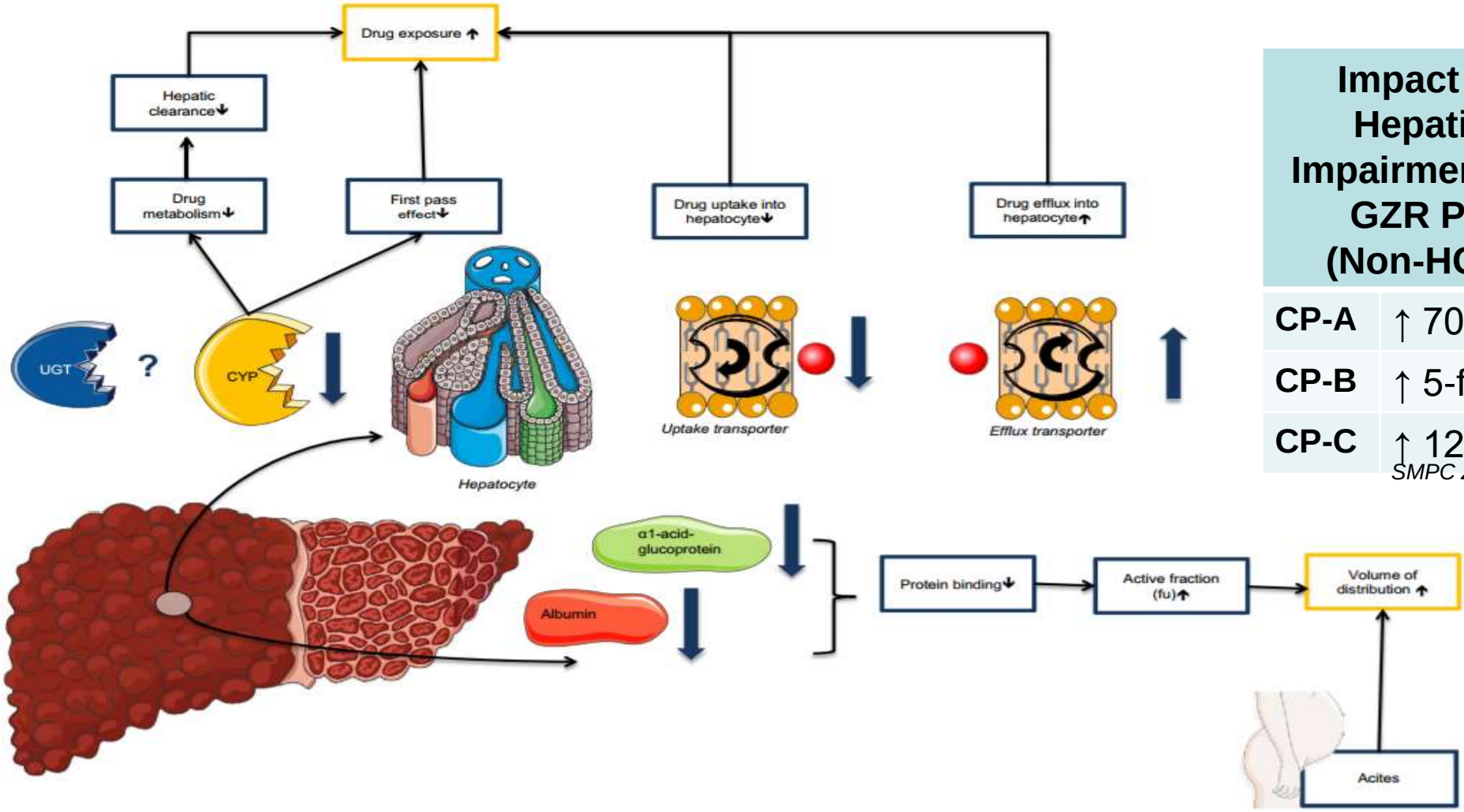
Non-Invasive Assessment of Liver Disease Severity

Test	Stage of fibrosis	Number of patients	Cutoff(s)	AUROC	Sensitivity	Specificity	PPV	NPV
FibroScan®	**F3**	560 HCV+	**10 kPa[a]**	0.83	72%	80%	62%	89%
	F4	HCV+	**13 kPa[a]**	0.90-0.93	72-77%	85-90%	42-56%	95-98%
ARFI (VTQ®)	**F3**	2691 (1428 HCV+)	**1.60-2.17 m/sec**	0.94* (0.91-0.95)	84%* (80-88%)	90%* (86-92%)	NA	NA
	F4	2691 (1428 HCV+)	**2.19-2.67 m/sec**	0.91* (0.89-0.94)	86%* (80-91%)	84%* (80-88%)	NA	NA
Aixplorer®	**F3**	379 HCV+	**9 kPa[a]**	0.91	90%* (72-100%)	77%* (78-92%)	NA	NA
	F4	379 HCV+	**13 kPa[a]**	0.93	86%* (74-95%)	88%* (72-98%)	NA	NA
Fibrotest®	**F4**	1579 (1295 HCV+)	**0.74**	0.82-0.87	63-71%	81-84%	39-40	93-94
FIB-4	**F4**	2297 HCV+	**1-45[b]** **3.25[b]**	0.87** (0.83-0.92)	90% 55%	58% 92%	NA	NA
APRI	**F4**	16,694 HCV+	**1.0[b]** **2.0[b]**	0.84** (0.54-0.97)	77% 48%	75% 94%	NA	NA

[a]Scales for liver stiffness cutoffs (in kPa) are different between FibroScan® and Aixplorer®.
[b]Two cutoffs are provided for FIB-4 and for APRI, respectively, with their own sensitivities and specificities.
***95%CI; ****median (range).**

(EASL Recommendations on Treatment of Hepatitis C 2018)

Disease Severity Impacts the PK of PIs



Impact of Hepatic Impairment on GZR PK (Non-HCV)	
CP-A	↑ 70%
CP-B	↑ 5-fold
CP-C	↑ 12-fold

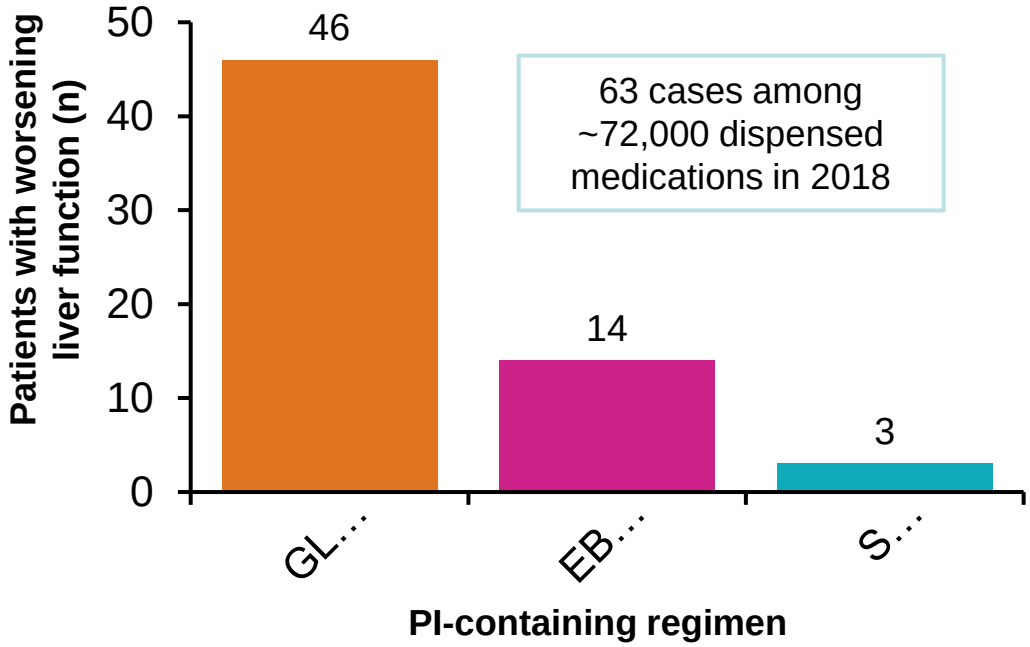
SMPC Zepatier

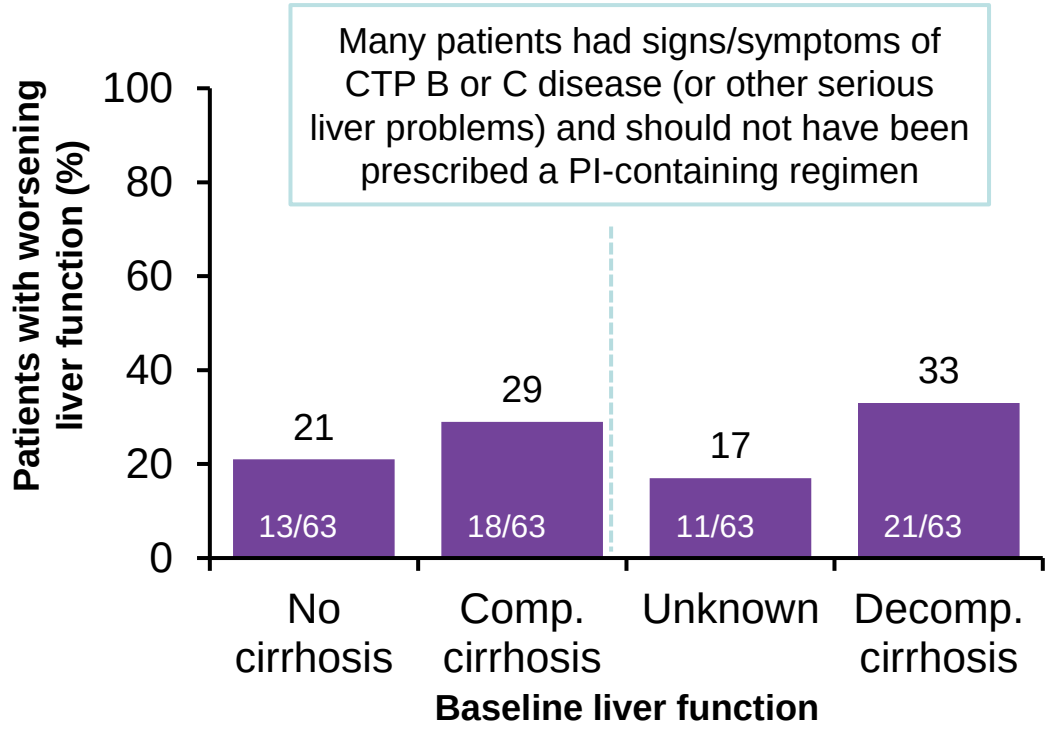
Fig. 2 Overview of the pathophysiological changes in patients with liver cirrhosis that influence drug metabolism and therefore the pharmacokinetics of drugs. *CYP* cytochrome P450, *UGT* uridine diphosphate-glucuronosyltransferase, ↓ indicates decrease, ↑ indicates increase

Drug Saf (2016) 39:589–611

Protease inhibitors are contraindicated in CTP B & C

Liver decompensation associated with DAA use in FAERS database or literature to 8 January 2019





US Food and Drug Administration. FDA Drug Safety Communication 28/08/2019. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and (accessed November 2020)

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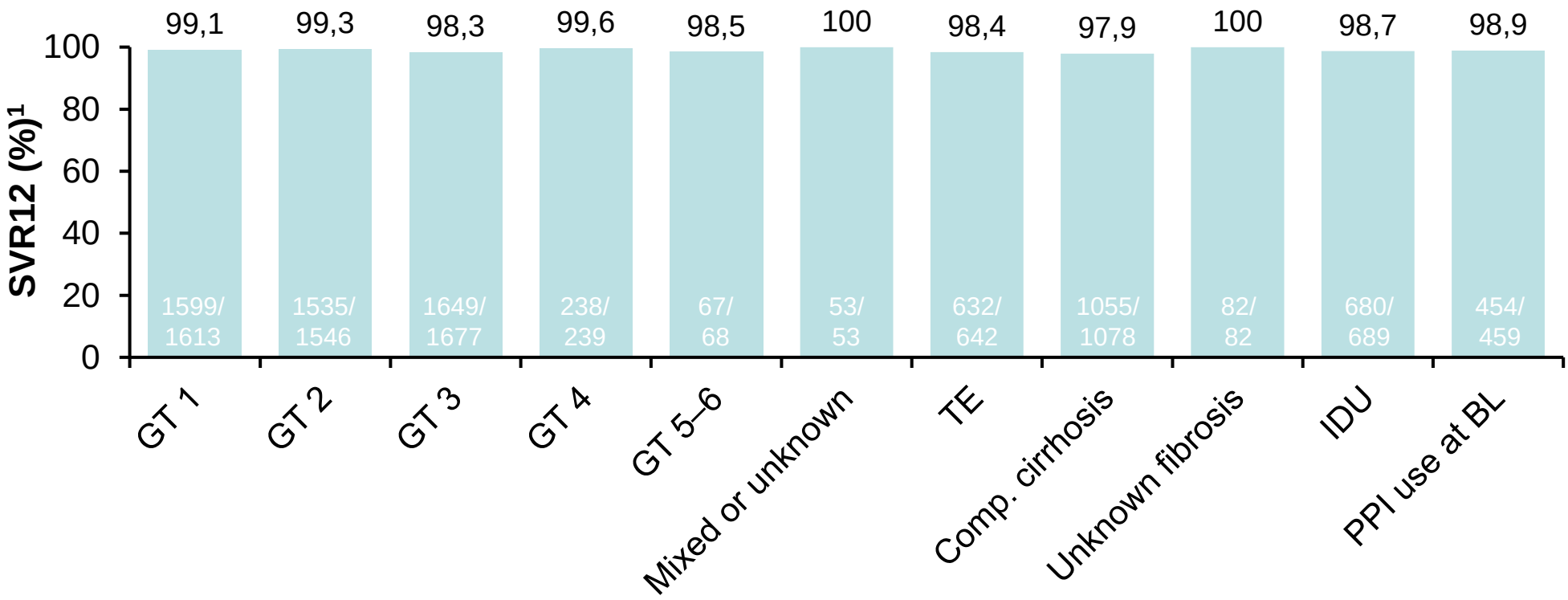
		Compensated (Child-Pugh A) cirrhosis)	Treatment-naïve				
			Treatment-experienced				

Easl 2020 HCV Treatment Recommendations, J Hepatol in press

Real-world experience with SOF/VEL for 12 weeks

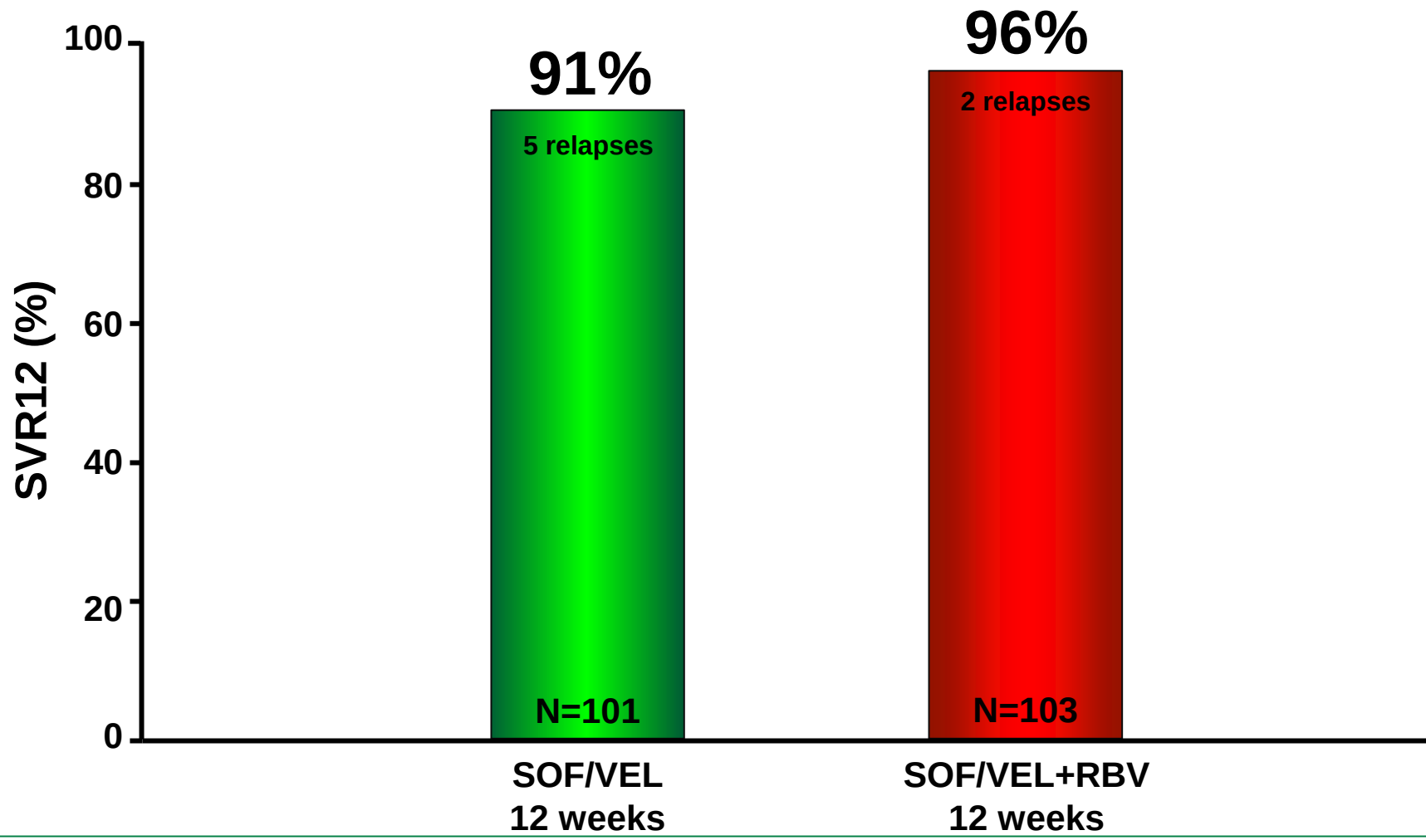


- Virological failures: **1% (55/5552)**[1]
- Non-virological failures: **6% (332/5552)** – of which 67% LTFU, 27% early D/C[1]
- **<1%** of patients discontinued treatment with SOF/VEL due to AEs in clinical trials[2]

1. Mangia A, et al. Liver Int 2020;40:1841–52;
2. Gilead Sciences. Epclusa (sofosbuvir/velpatasvir). SmPC. September 2020

Sofosbuvir/Velpatasvir ± RBV

Randomized trial in patients with cirrhosis



Esteban R Gastroenterology 2019

EASL HCV Treatment Algorithm for TN/TE Patients Without Cirrhosis or With Compensated Cirrhosis

Treatment recommendations for HCV-mono-infected or HCV/HIV coinfected adult (aged ≥18 years) and adolescent (aged 12–17 years) patients with chronic HCV without cirrhosis or with CC* including TN and TE†

		Treatment-naïve		Treatment experienced	
		G/P	SOF/VEL	G/P	SOF/VEL
GT 1a, 1b, 2, 4, 5, and 6	**Without cirrhosis**	8 weeks	12 weeks	8 weeks	12 weeks
	With compensated cirrhotic	8 weeks	12 weeks	12 weeks	12 weeks
GT 3	**Without cirrhosis**	8 weeks	12 weeks	12 weeks	12 weeks
	With compensated cirrhotic	8–12 weeks‡	12 weeks with weight-based RBV§	16 weeks	12 weeks with weight-based RBV§

- *Child-Pugh A; †TE to pegIFN + RBV, pegIFN-α + RBV + SOF or SOF + RBV; ‡In TN patients infected with GT3 with CC, treatment with G/P can be shortened to 8 weeks, but more data are needed to consolidate this recommendation; § If resistance testing is formed, only patients with the NS5A Y93H RAS at baseline should be treated with SOF/VEL + RBV or with SOF/VEL/VOX, whereas patients without the Y93H RAS should be treated with SOF/VEL alone.
  CC, compensated cirrhosis; EASL, European Association for the Study of the Liver; G/P, glecaprevir/pibrentasvir; GT, genotype; pegIFN, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; TE, treatment experienced; TN, treatment-naïve; VEL, velpatasvir.

1. EASL. *J Hepatol* 2020 Nov;73(5):1170-1218. doi: 10.1016/j.jhep.2020.08.018. Epub 2020 Sep 15. 2. Maviret (GLE/PIB) US Prescribing Information.

Efficacy and Safety of 8-Week G/P in Treatment-Naive Patients with Chronic Hepatitis C Virus GT1–6 Infection and Compensated Cirrhosis: EXPEDITION-8 Complete Results

A single arm, open-label, Phase 3b, multicenter study to assess the safety and efficacy of G/P for 8 weeks in HCV GT1–6-infected treatment-naive patients with compensated cirrhosis (N = 343)

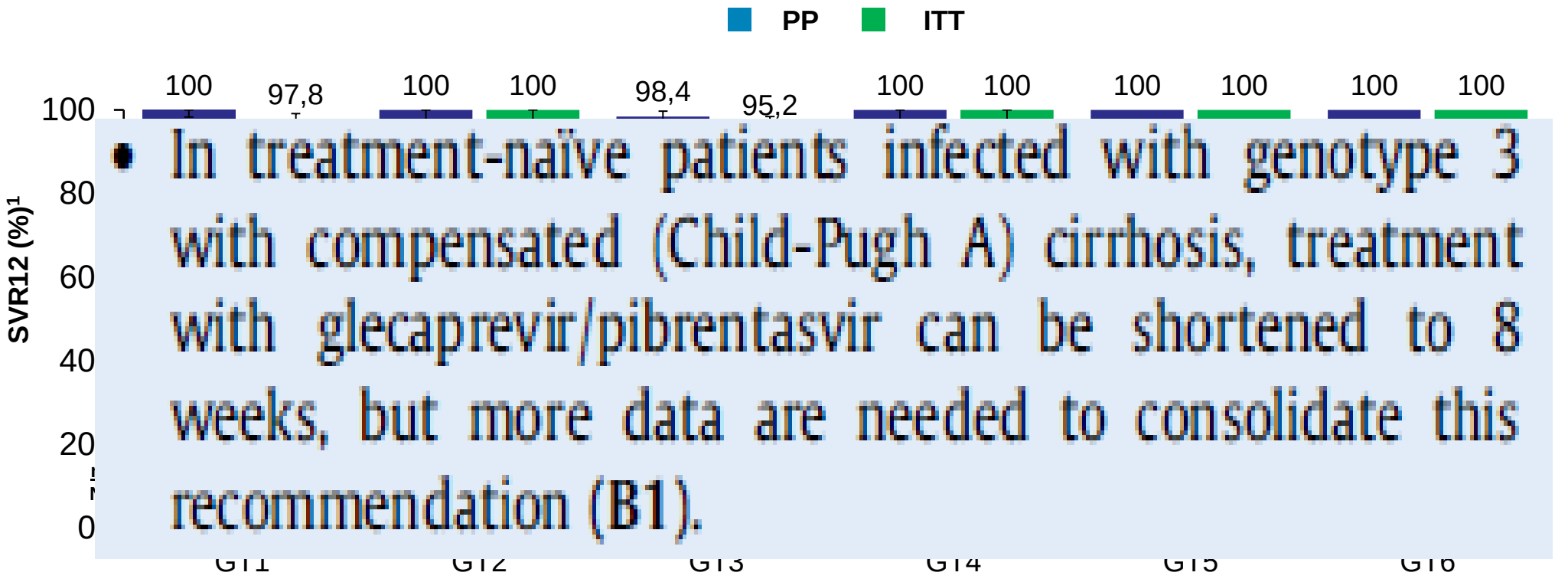
Baseline characteristics	N = 343
Male, n (%)	217 (63)
Age, median years (IQR)	58 (51–65)
White, n (%)	285 (83)
Genotype, n (%) 1 2 3 4 / 5 / 6	 231 (67) 26 (8) 63 (18) 13 (4) / 1 (<1) / 9 (3)
FibroScan® score, median (IQR)†	20.2 (16.4–26.6)
Child-Pugh score, n (%) 5 6 >6	 307 (90) 33 (10) 3 (<1)*
Patients with IDU,§ n (%)	92 (27)
Patients on stable OST, n (%)	27 (8)

Baseline characteristics	N = 343
Albumin, median (IQR), g/dL	4.2 (4–4.5)
Total bilirubin, median (IQR), µmol/L	12.0 (8.6–16)
Alanine aminotransferase, median (IQR), U/L	78 (49–116)
Platelet count × 10^9/L, median (IQR)	151 (110–188)

- * 3 patients had a Child-Pugh score of 7 at baseline (2 had a score ≤6 at screening; 1 protocol deviation had a score of 7);
  † n = 295 patients had Fibroscan score data available; ‡ n = 335 patients had resistance testing available; § All but 4 patients reported injection drug use >12 months ago.
  IDU, injection drug use; IQR, inter-quartile range; OST, opioid substitution therapy.

- Brown RS, et al. J Hepatol 2020].

Efficacy and Safety of 8-Week G/P in Treatment-Naive Patients with Chronic Hepatitis C Virus GT1–6 Infection and Compensated Cirrhosis: EXPEDITION-8 Complete Results



- In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 weeks, but more data are needed to consolidate this recommendation (B1).

All patients with baseline NS3 and NS5A achieved SVR

Based on these data, the EMA Label now includes an 8 week duration for GT1–6 TN CC patients

- Brown RS, et al. J Hepatol 2020].

Treatment of HCV Patients with Cirrhosis: Outline

- Indication to Treatment (Who to Treat?)
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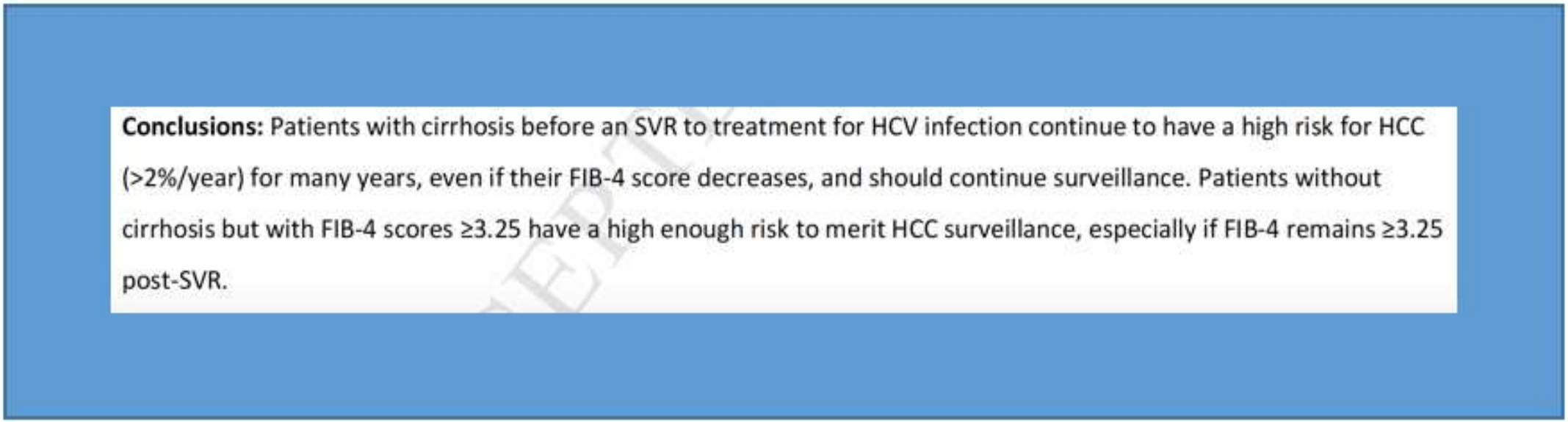
Increased Risk of HCC Persists up to 10 Years After Virus Eradication in Patients with Advanced HCV

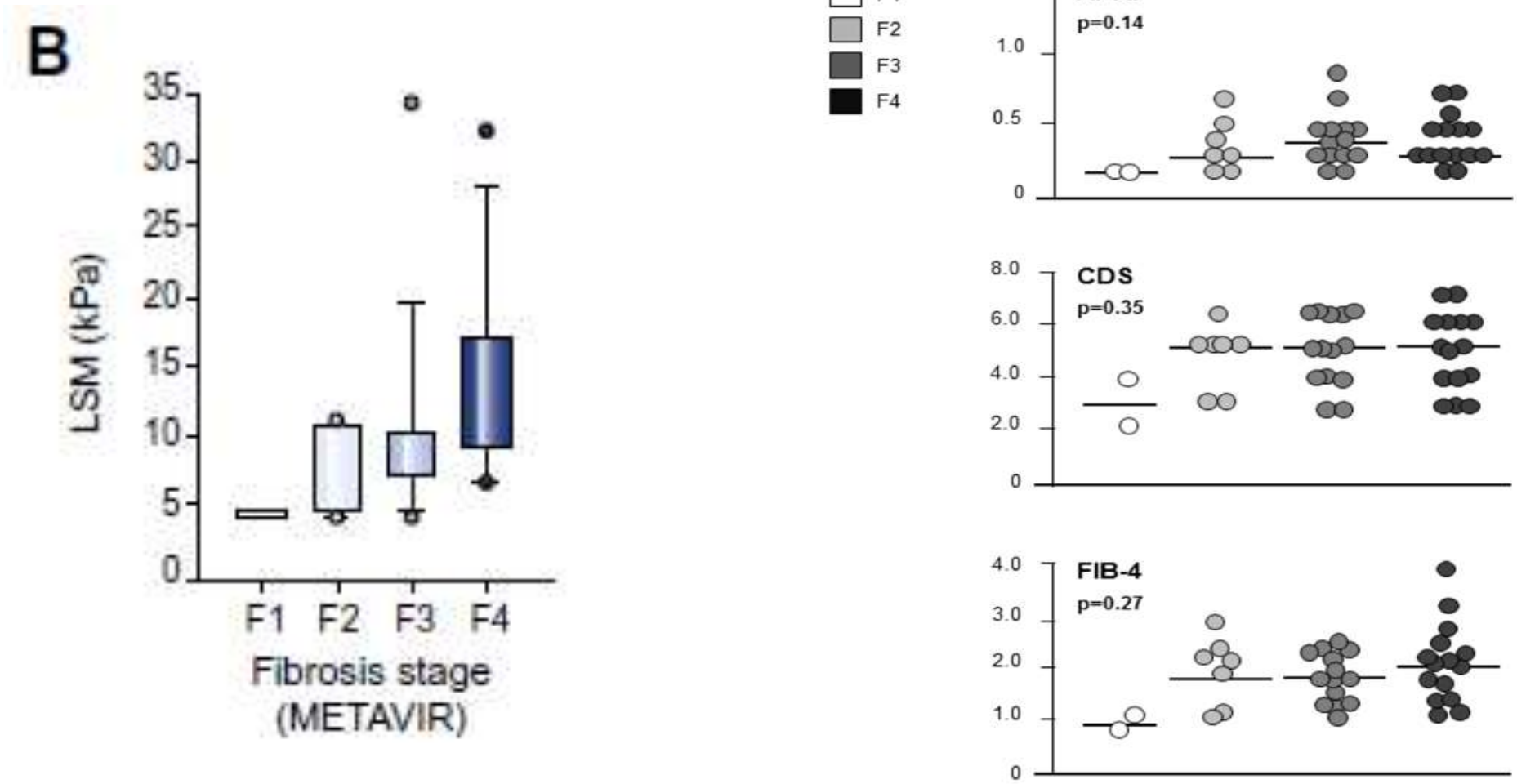
- 29,033 VA patients with an SVR to DAA and 19,102 with an SVR to IFN
- During 5.4 yr follow-up, 1509 incident HCCs were identified

Conclusions: Patients with cirrhosis before an SVR to treatment for HCV infection continue to have a high risk for HCC (>2%/year) for many years, even if their FIB-4 score decreases, and should continue surveillance. Patients without cirrhosis but with FIB-4 scores ≥3.25 have a high enough risk to merit HCC surveillance, especially if FIB-4 remains ≥3.25 post-SVR.



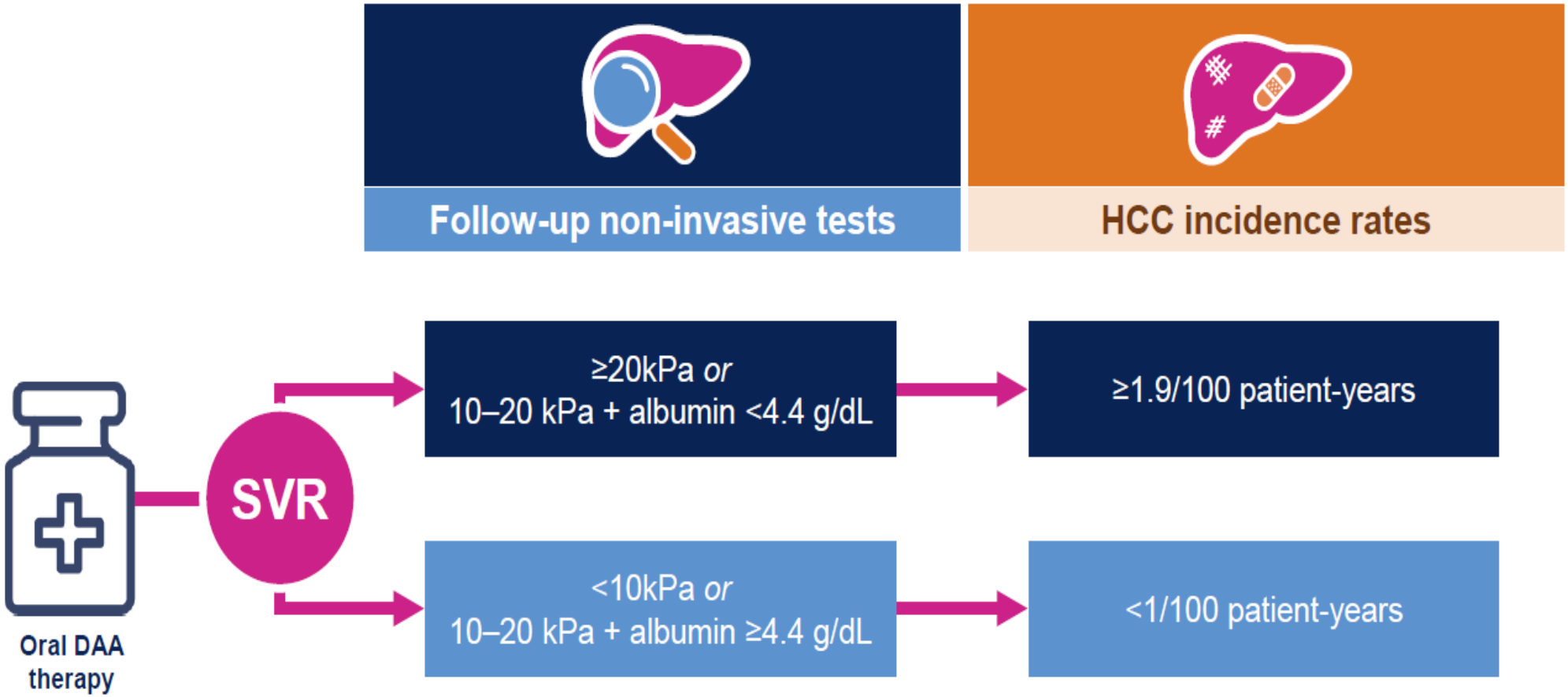
Ioannou GN et al Hepatology 2019

Non Invasive Methods Are Inaccurate in Assessing Post SVR Fibrosis Regression



D'Ambrosio R et al J Hepatol 2013 and Plos One 2016

Non Invasive Methods to Identify Patients at High Risk of HCC



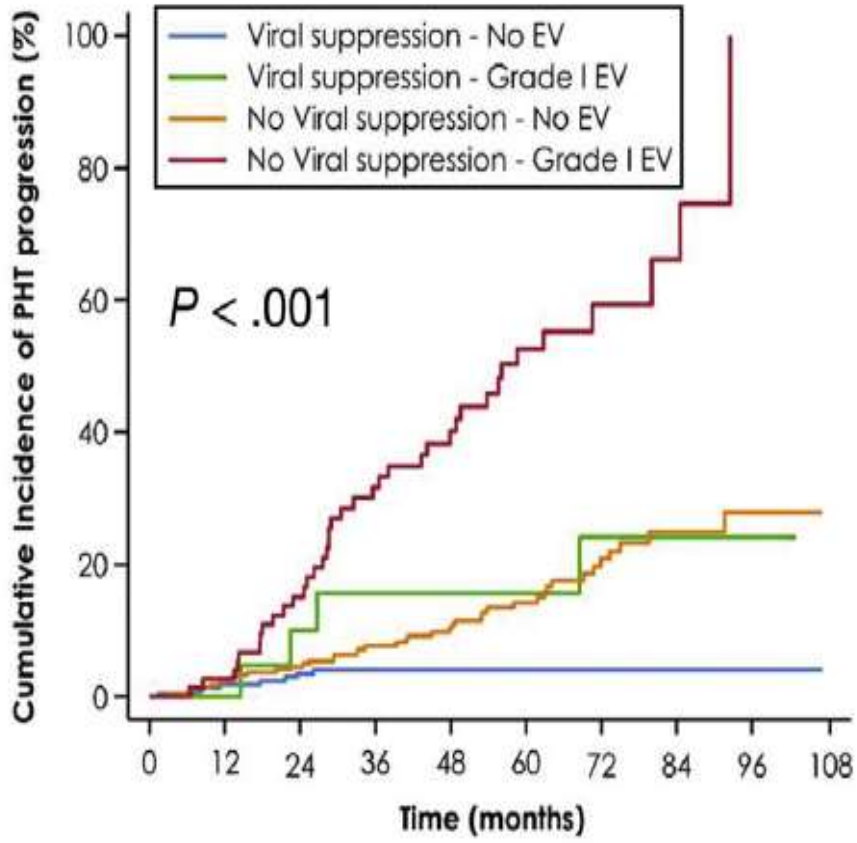
572 patients treated with DAAs and achieved SVR. All patients had LSM ≥10 kPa before treatment with no history of decompensation. Median follow-up 2.8 years. HCC occurred in 25 patients during the follow-up period. LSM: liver stiffness measure; SVR: sustained virological response

Pons M et al. J Hepatol 2020; 72: 472–480

Long-term follow-up – varices

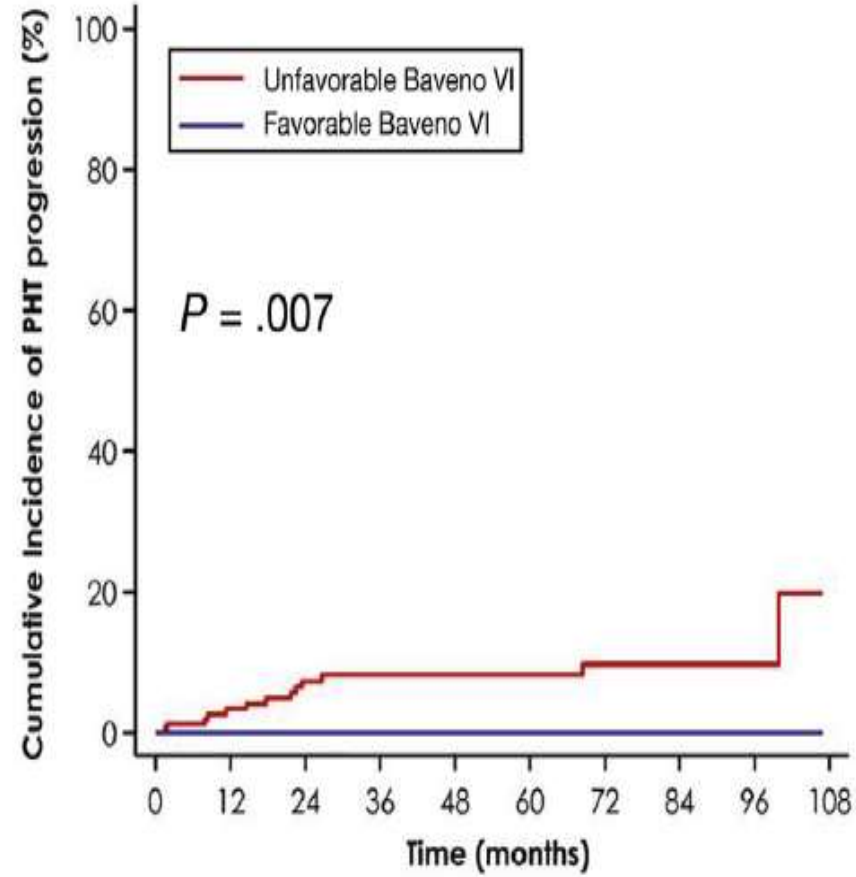
World Health Organization	No specific follow-up recommendations given	**Endoscopy every 1–2 years to exclude oesophageal varices**
EASL European Association for the Study of the Liver	Discharge provided they have no further comorbidities	**Surveillance by endoscopy should be performed if varices were 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**

Management of Portal Hypertension Following Viral Suppression



Number at risk (events)

Viral suppression - No EV	246	(4)	201	(3)	170	(1)	151	(0)	133	(0)	114	(0)	85	(0)	58	(0)	34	(0)	5
Viral suppression - Grade I EV	27	(0)	23	(2)	16	(1)	13	(0)	10	(0)	10	(1)	9	(0)	4	(0)	2	(0)	0
No Viral suppression - No EV	291	(6)	256	(6)	227	(7)	193	(5)	158	(6)	108	(7)	71	(3)	40	(1)	21	(0)	2
No Viral suppression - Grade I EV	75	(2)	72	(9)	59	(11)	43	(5)	32	(6)	21	(2)	8	(1)	5	(2)	0	(0)	0

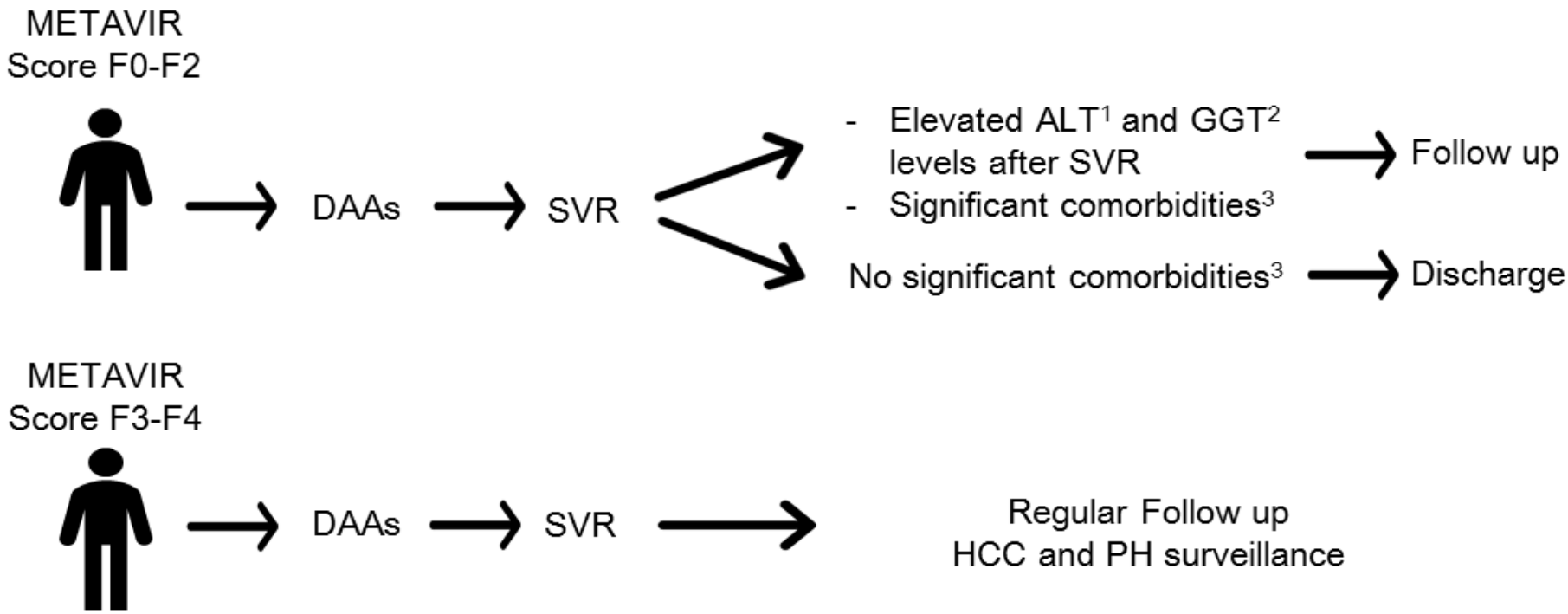


Number at risk (events)

Unfavorable Baveno VI	164	(5)	135	(5)	112	(1)	98	(0)	84	(0)	72	(1)	53	(0)	32	(0)	16	(1)	2
Favorable Baveno VI	64	(0)	63	(0)	59	(0)	58	(0)	55	(0)	50	(0)	43	(0)	32	(0)	22	(0)	3

Thabut D et al, Gastroenterology 2019

Who Should We Follow-up Post SVR



1 elevated ALT levels: ≥ 35 U/L for females, ≥50 U/L for males 2. elevated GGT levels : 40 U/L for females, ≥ 60 U/L for males 3. Non alcoholic steato hepatitis, obesity, alcohol consumption and diabetes

Colapietro F, Aghemo A, Liver International 2020