17th Residential Course on Clinical Pharmacology of Antiretrovirals

HCV Treatment of Patients with Cirrhosis

Alessio Aghemo, MD, PhD

Department of Biomedical Sciences, Humanitas University
Division of Internal Medicine and Hepatology, Department of Gastroenterology
Humanitas Research Hospital, Rozzano, Italy

Financial Disclosures

Grant and research support:	AbbVie, Gilead Sciences
Advisory committees:	Merck, Gilead Sciences, AbbVie, Mylan, Sobi, Intercept and Alfasigma
Speaking and teaching:	Gilead Sciences, Abbvie, Mylan, Sobi, Alfasigma

Liver cirrhosis

Key information for clinicians from the *Lancet* Seminar

Risk factors

Proportion of population with the corresponding risk factor who will receive a diagnosis of cirrhosis at any time in their life

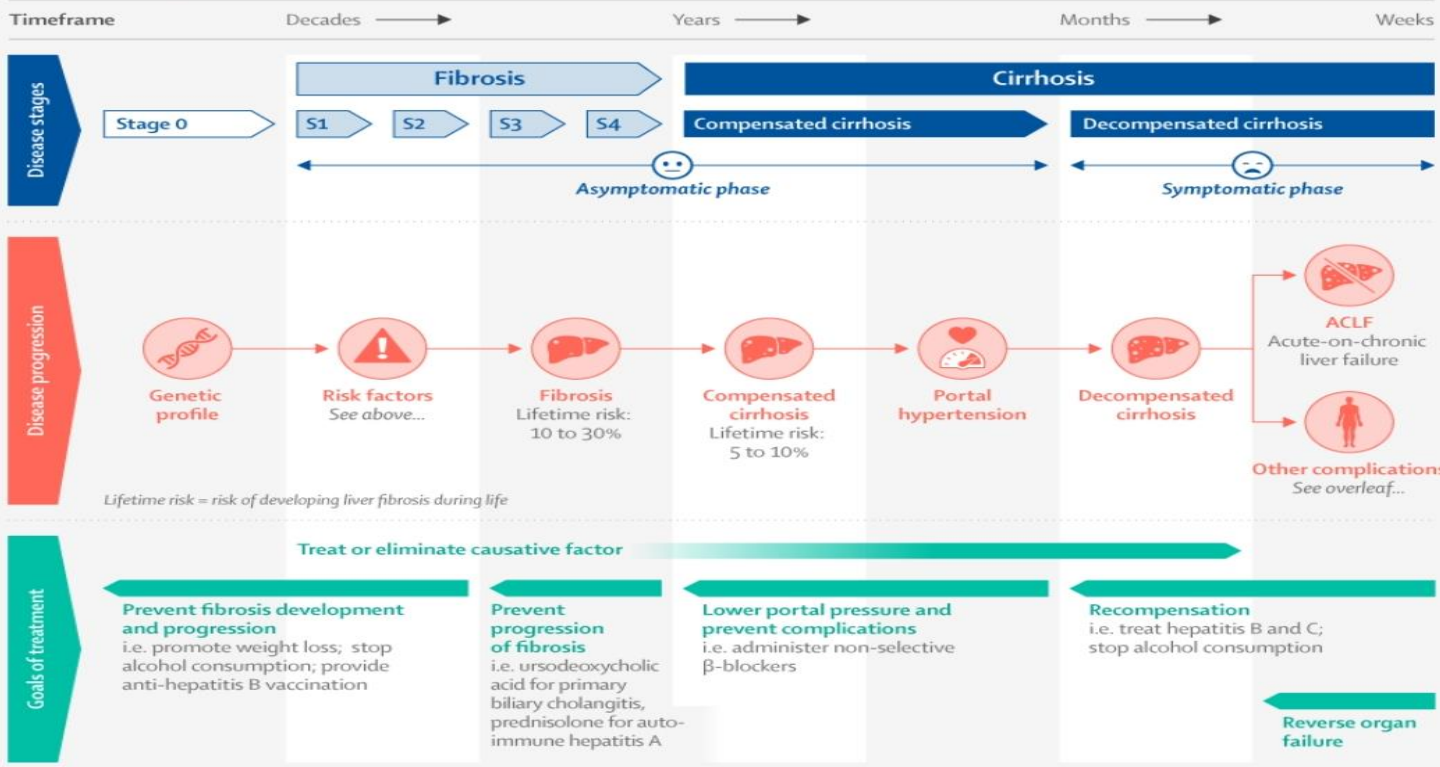
Alcohol consumption	5 to 10%
Obesity / Type 2 diabetes	1 to 2%
Hepitits B*	up to 40%
Hepitits C*	10 to 20%

**If left untreated*

More than 75 million people are at risk of alcohol-related liver disease due to **high alcohol consumption.**

Approximately 2 billion adults worldwide who are obese or overweight, and **400 million adults** worldwide who have diabetes, are also at risk of **non-alcoholic fatty liver disease.**

Natural progression of disease



Read the full seminar: https://www.thelancet.com/clinical/diseases/liver-cirrhosis

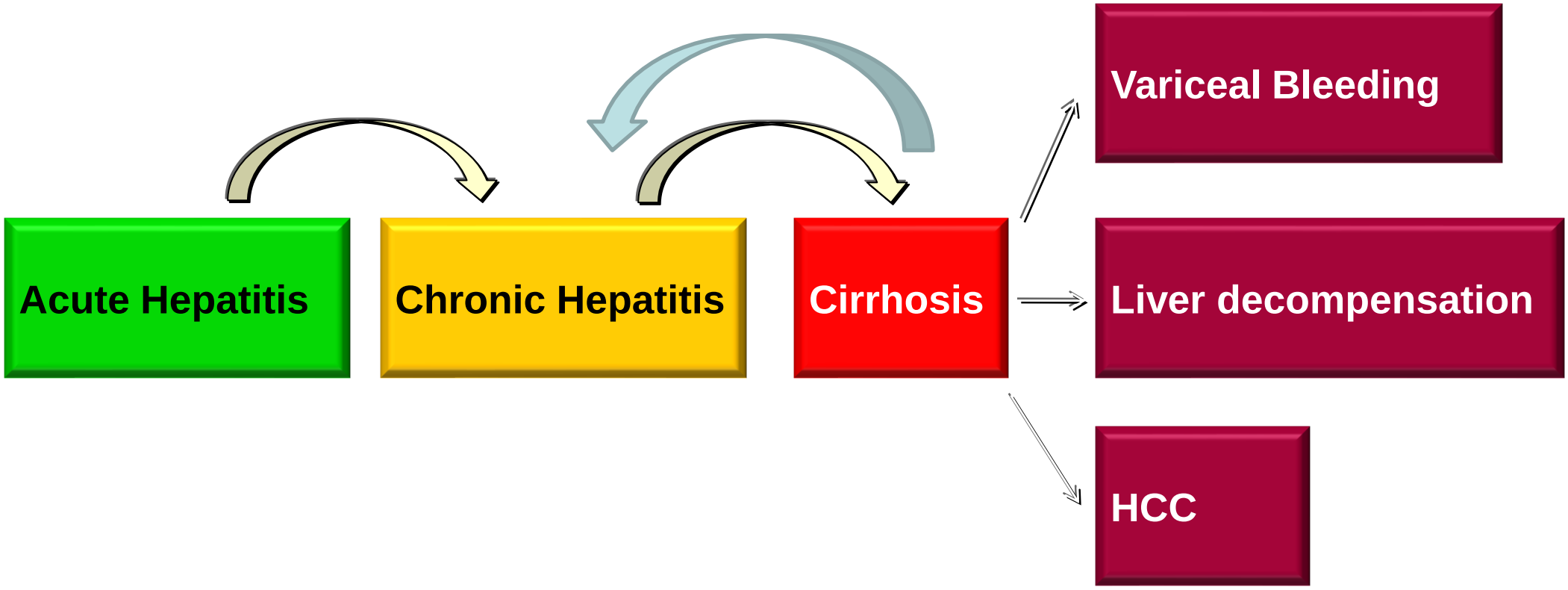
Treatment of HCV Patients with Cirrhosis: Outline

- Indication to Treatment (Who to Treat?)
- Treatment recommendations (How to Treat?)

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

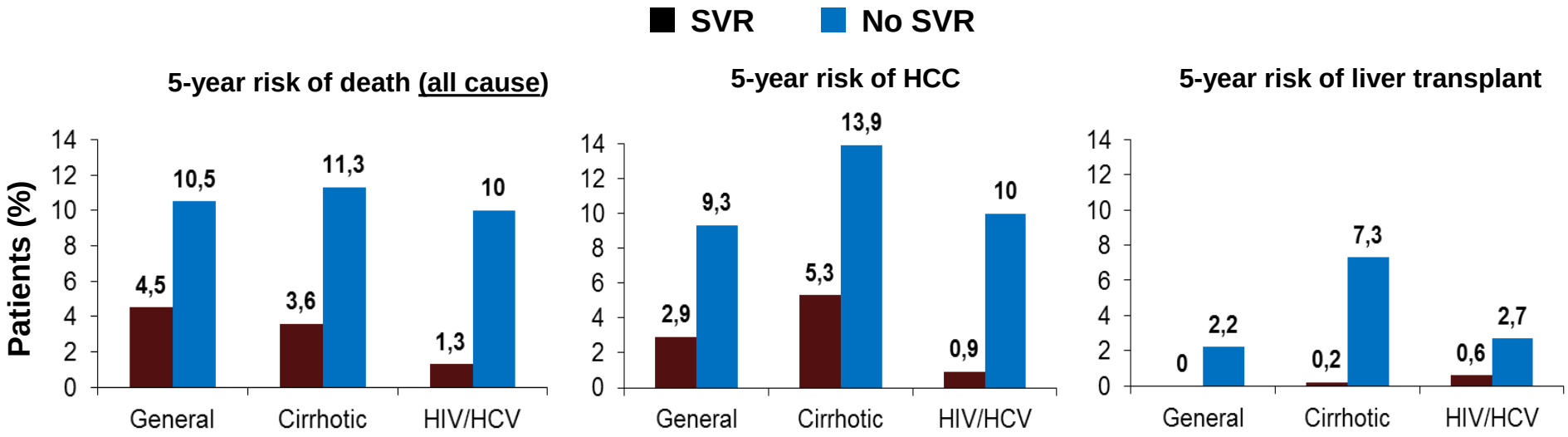
Natural History of Hepatitis C



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:

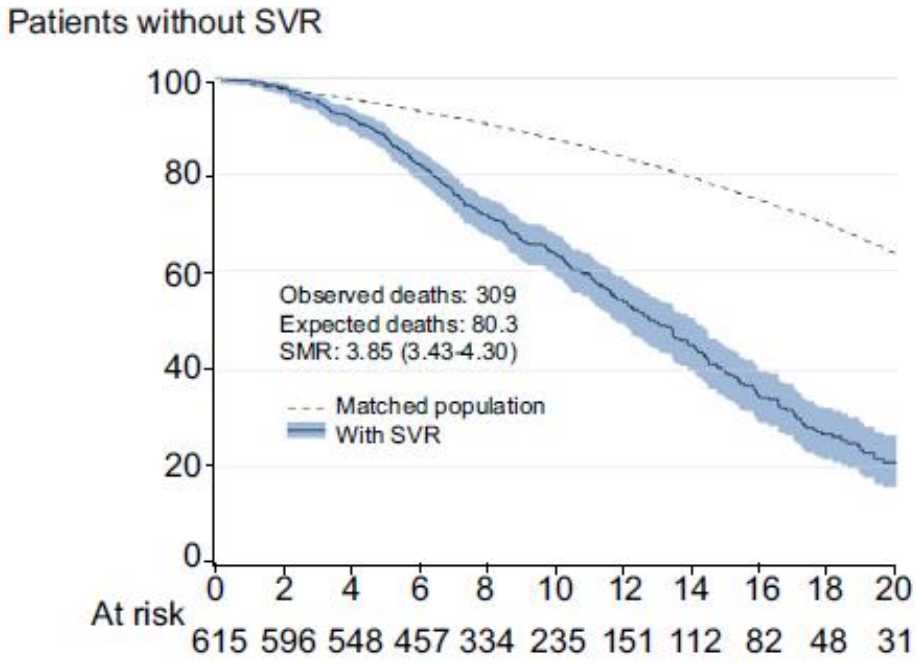
62–84% reduction in all-cause mortality

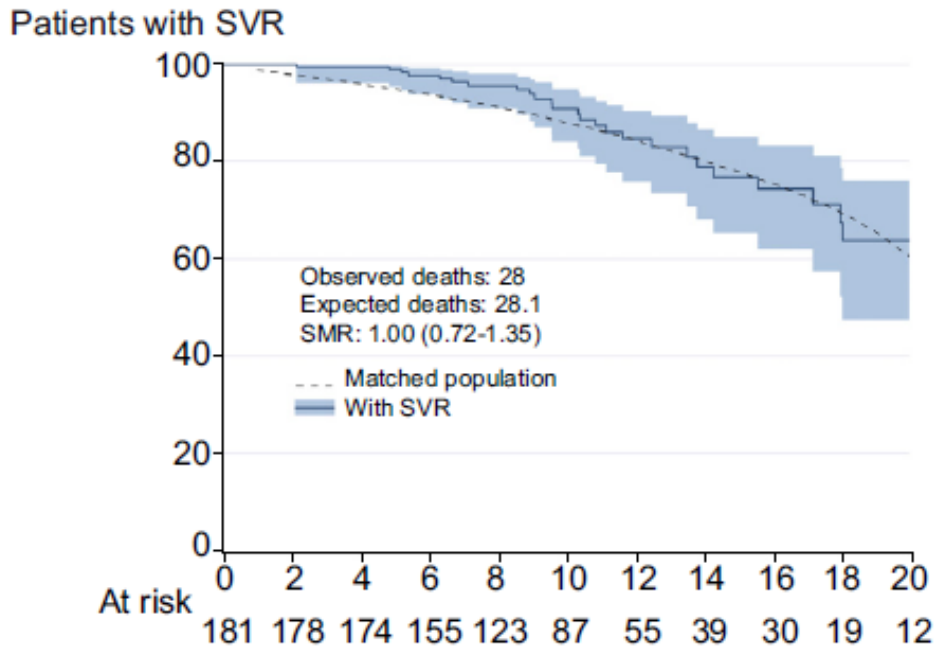
68–79% reduction in risk of HCC

90% reduction in risk of liver transplant

Saleem J, et al. Hepatology 2014

Survival of HCV Cirrhotics with an SVR is Comparable to the General Population

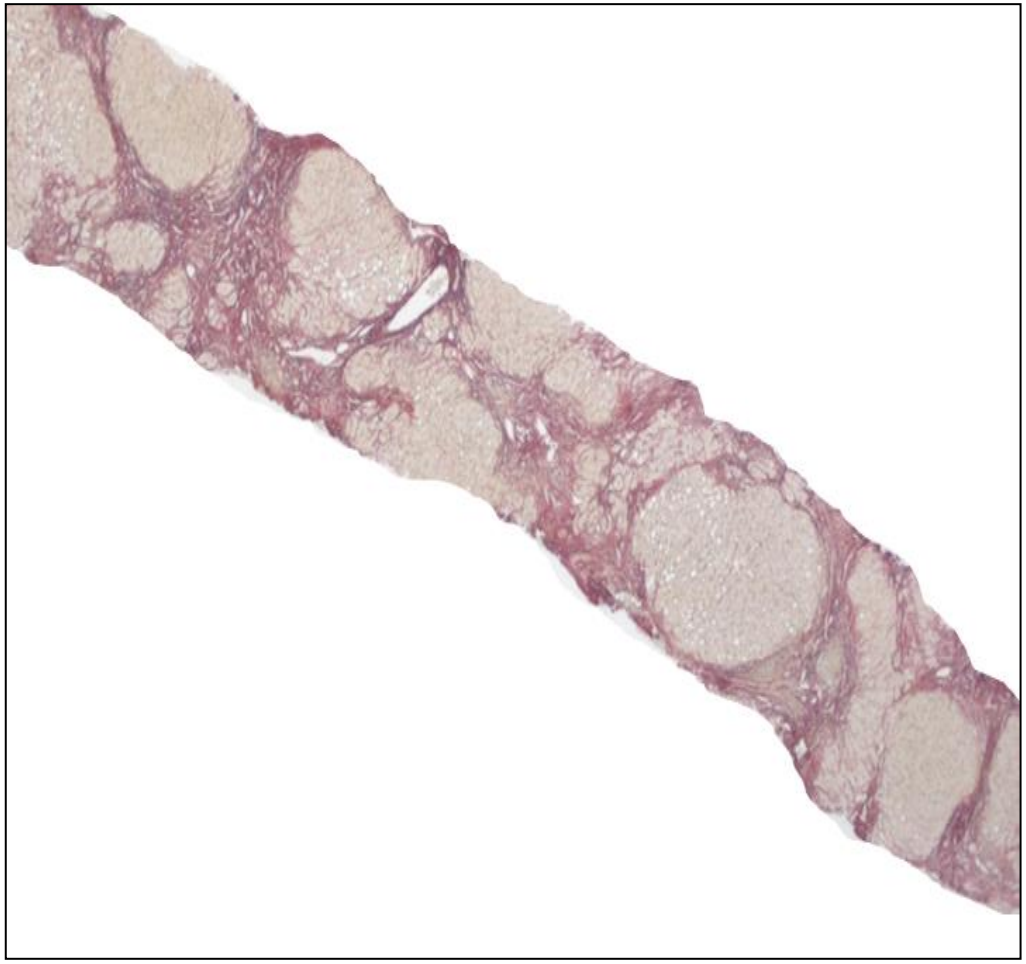




Bruno S et al J Hepatol 2017

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

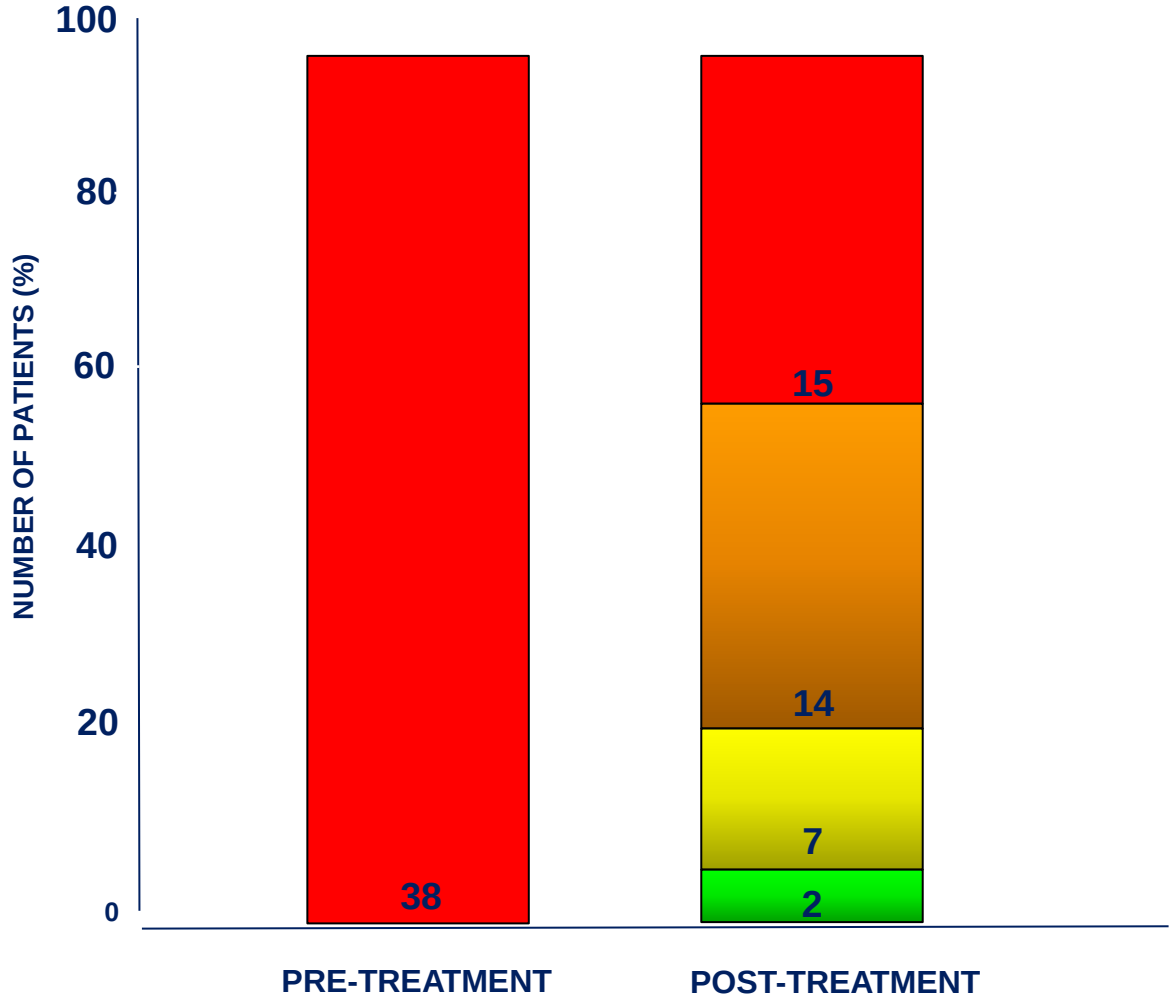
Pre-TX

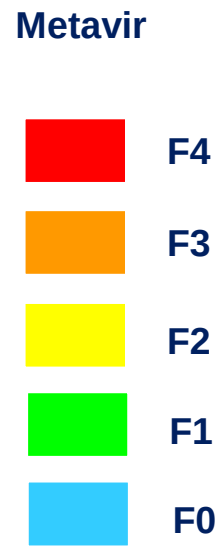


5 years post-SVR

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

Rates of Cirrhosis Regression According to the METAVIR Scoring System



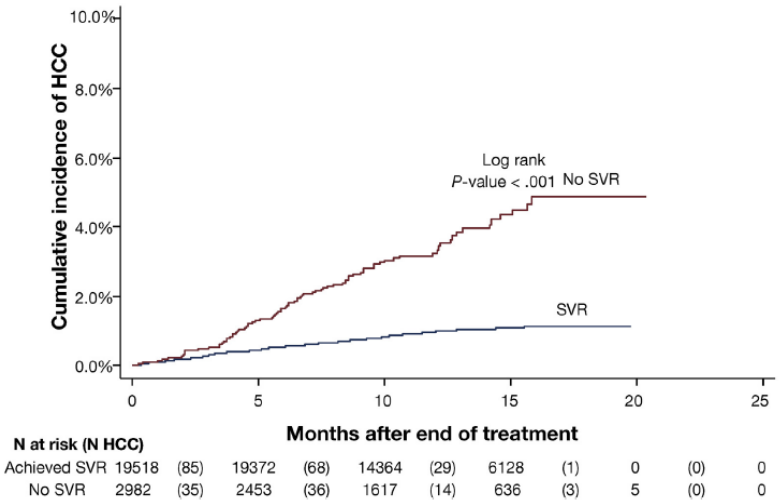


Cirrhosis Regression in 23 (61%) Patients

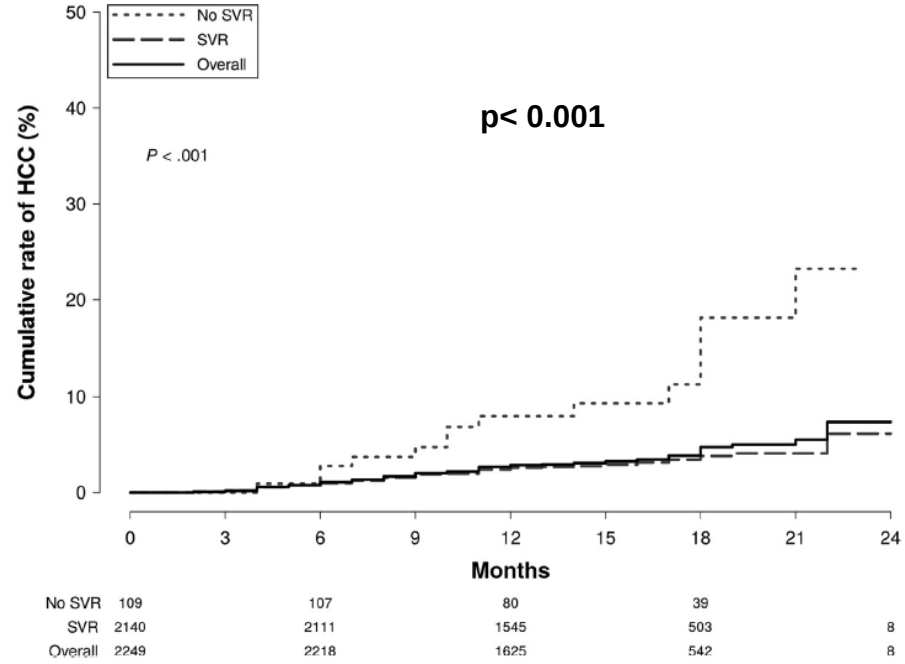
D'Ambrosio R et al Hepatology 2012, 56(2):532-43

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

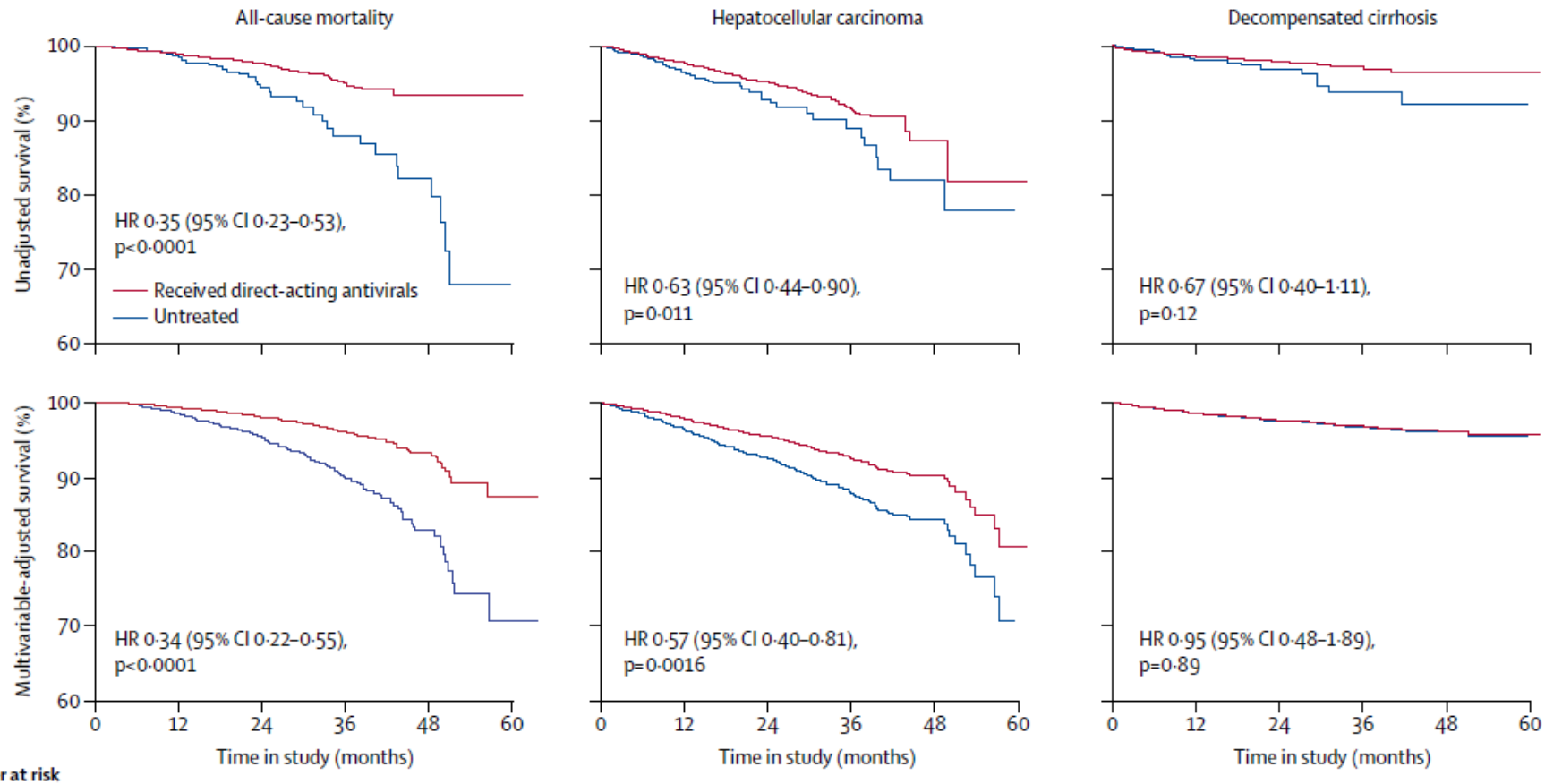


Calvaruso et al. Gastroenterology 2018

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.

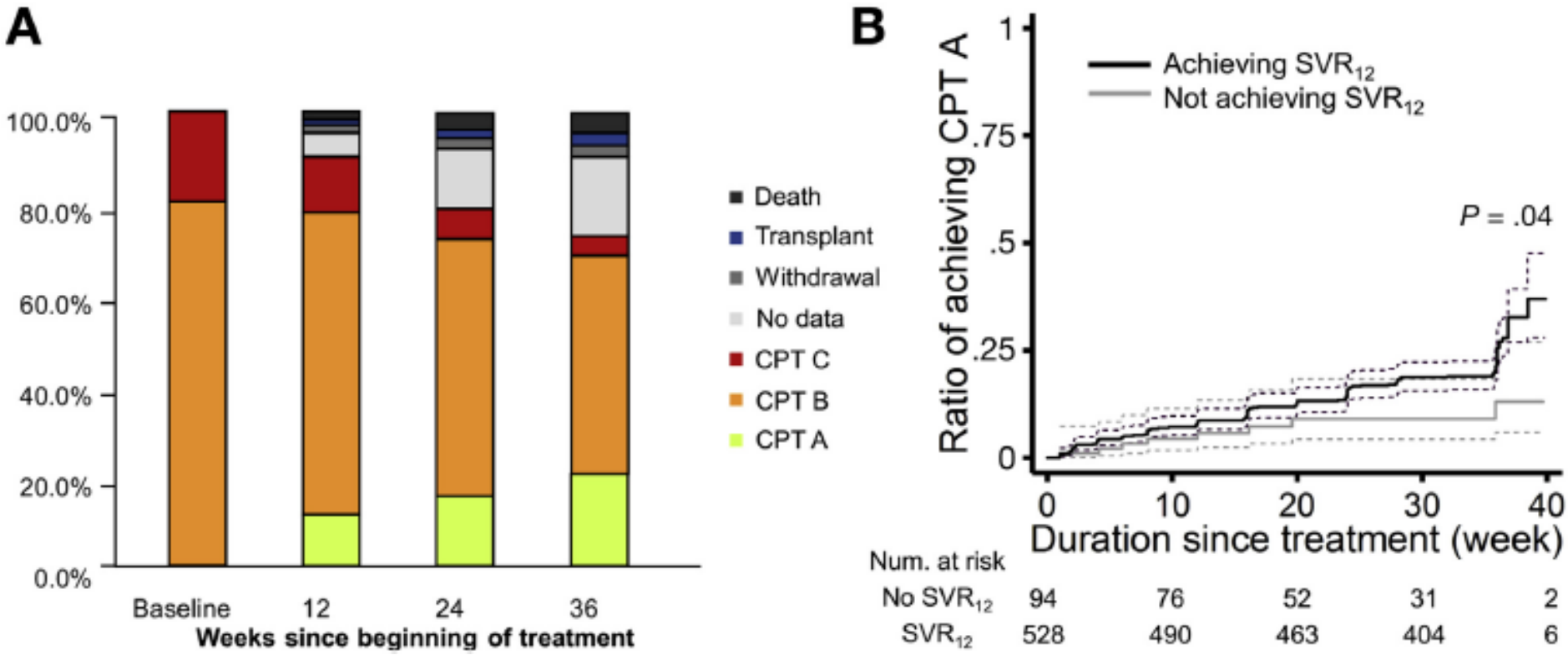
DAA Treatment Improves Survival in HCV Cirhosis



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)

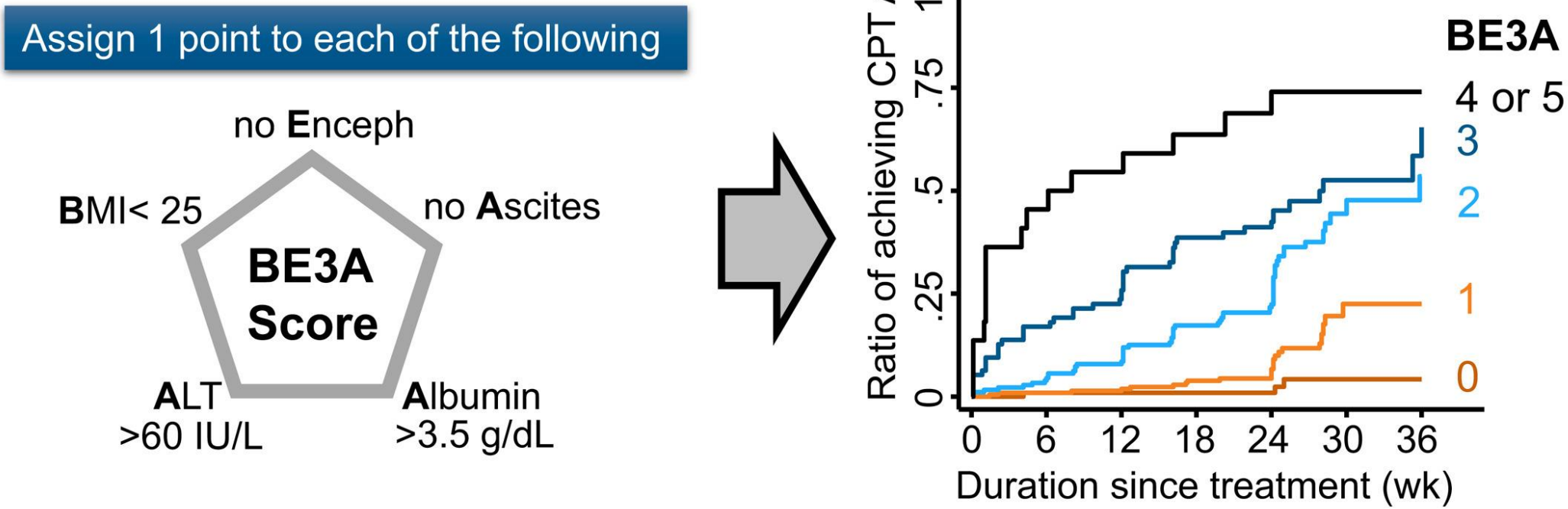
Carrat et al, Lancet 2019

Outcome of Decompensated HCV Cirrhosis After SVR



El Sherif O et al Gastroenterology 2018

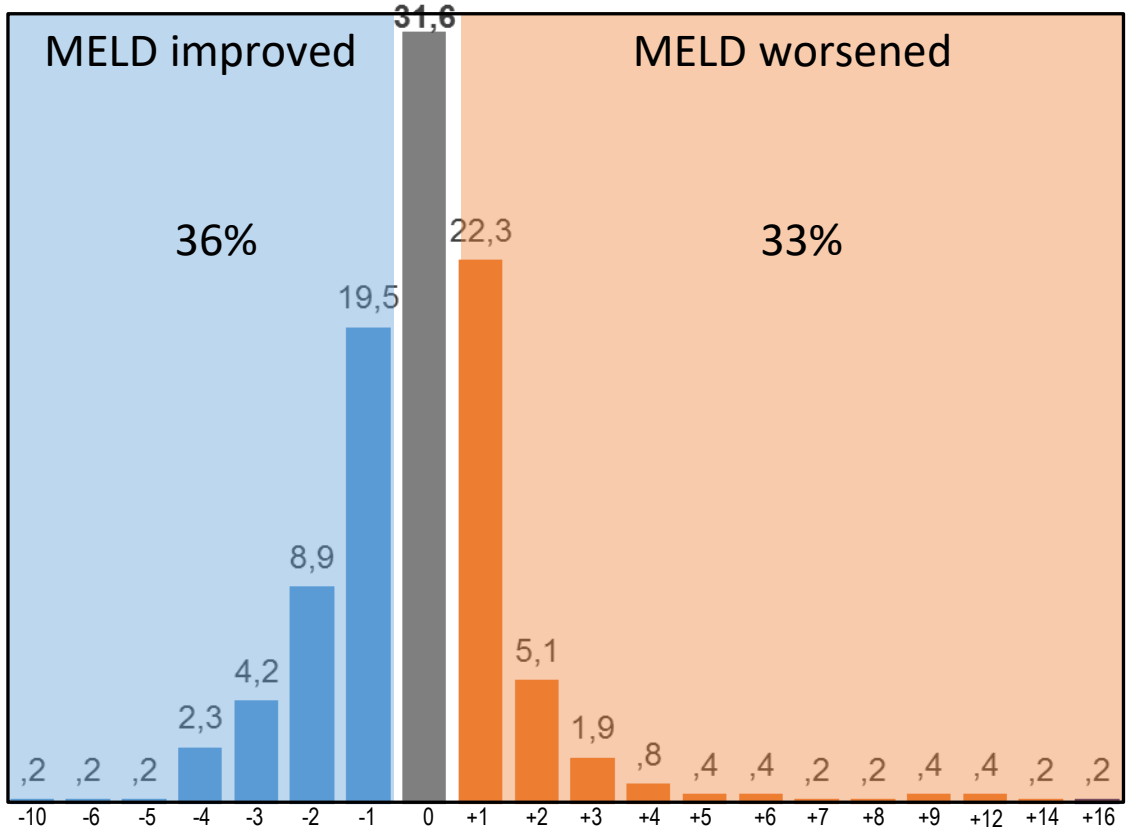
Outcome of Decompensated HCV Cirrhosis After SVR

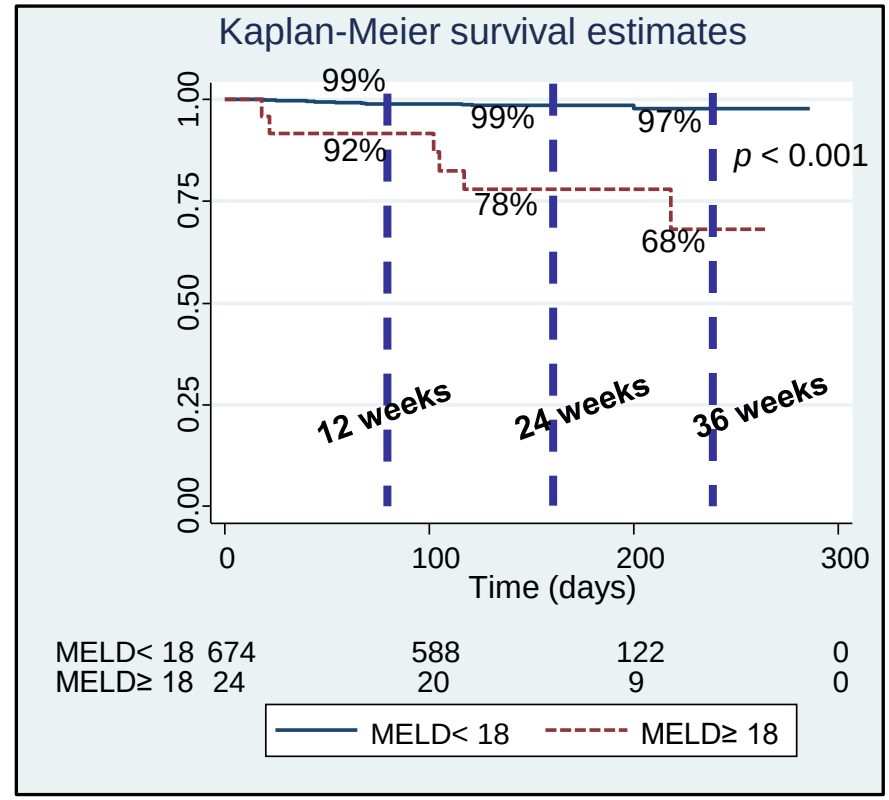


El Sherif O et al Gastroenterology 2018

Treatment of Hepatitis C Virus in Patients With Advanced Cirrhosis. The Hepa-C Registry

Deaths 16 (2%), Breakthroughs 9 (1%), Relapses 45 (7%)

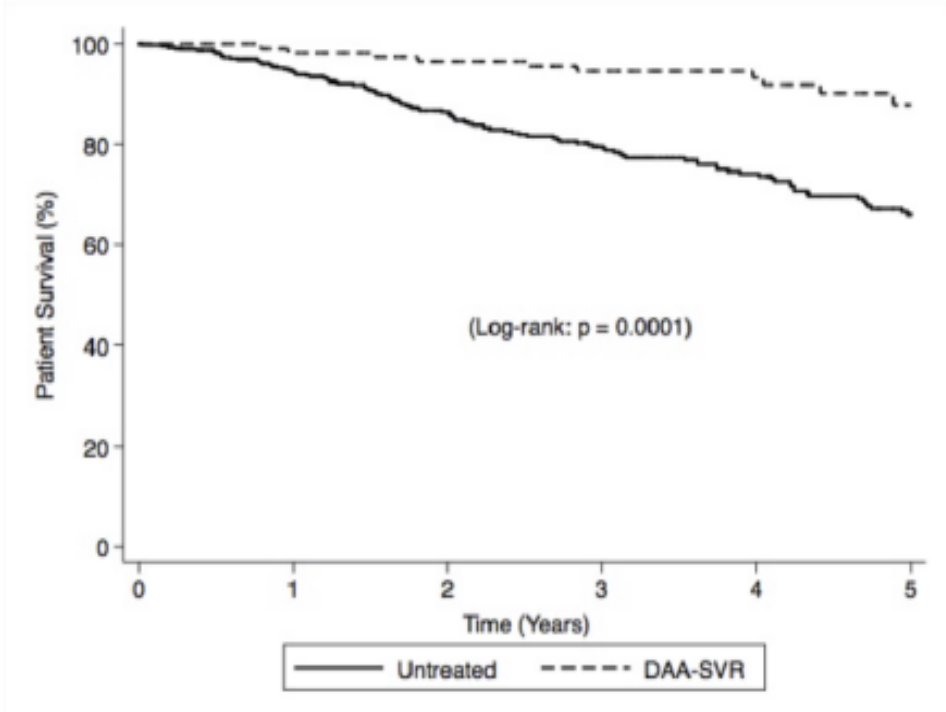




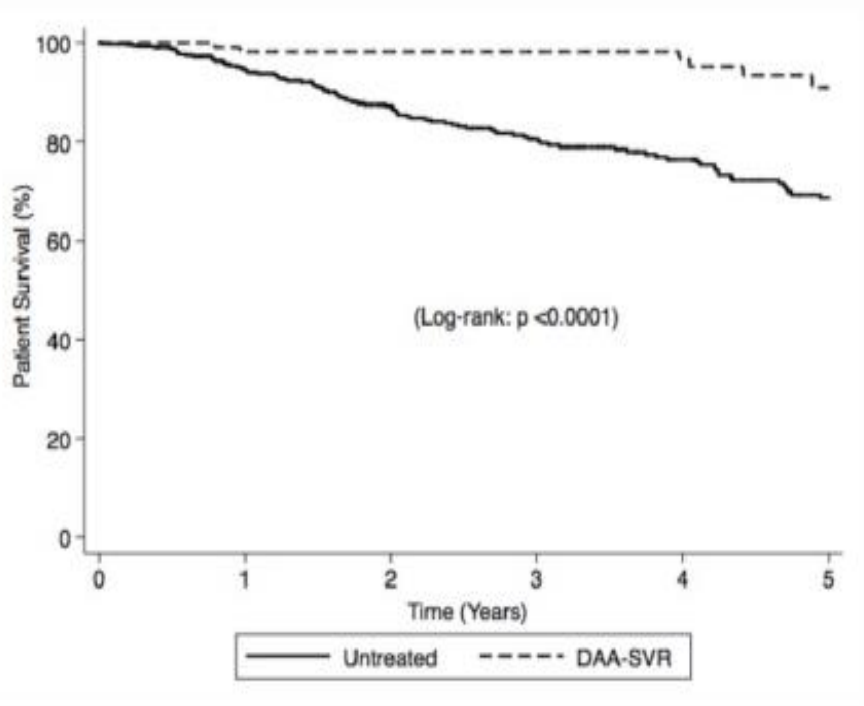
Calleja JL et al, J Hepatol 2017

Improved Survival of HCV Patients with HCC Who Received DAAs

Overall Mortality

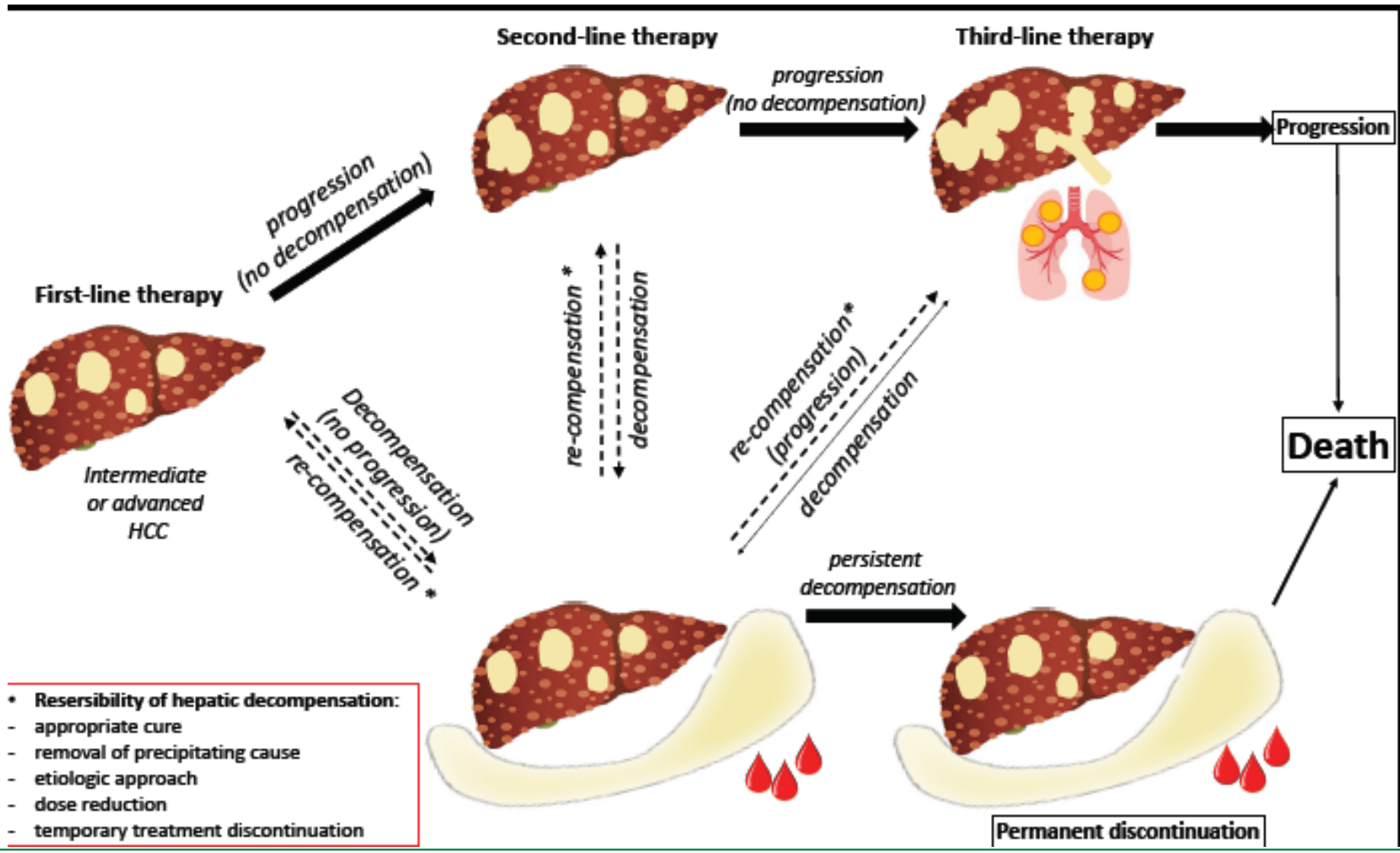


Liver related Mortality



Dang S et al, Hepatology 2020

Anti-HCV Treatment in Patients with HCC in 2022

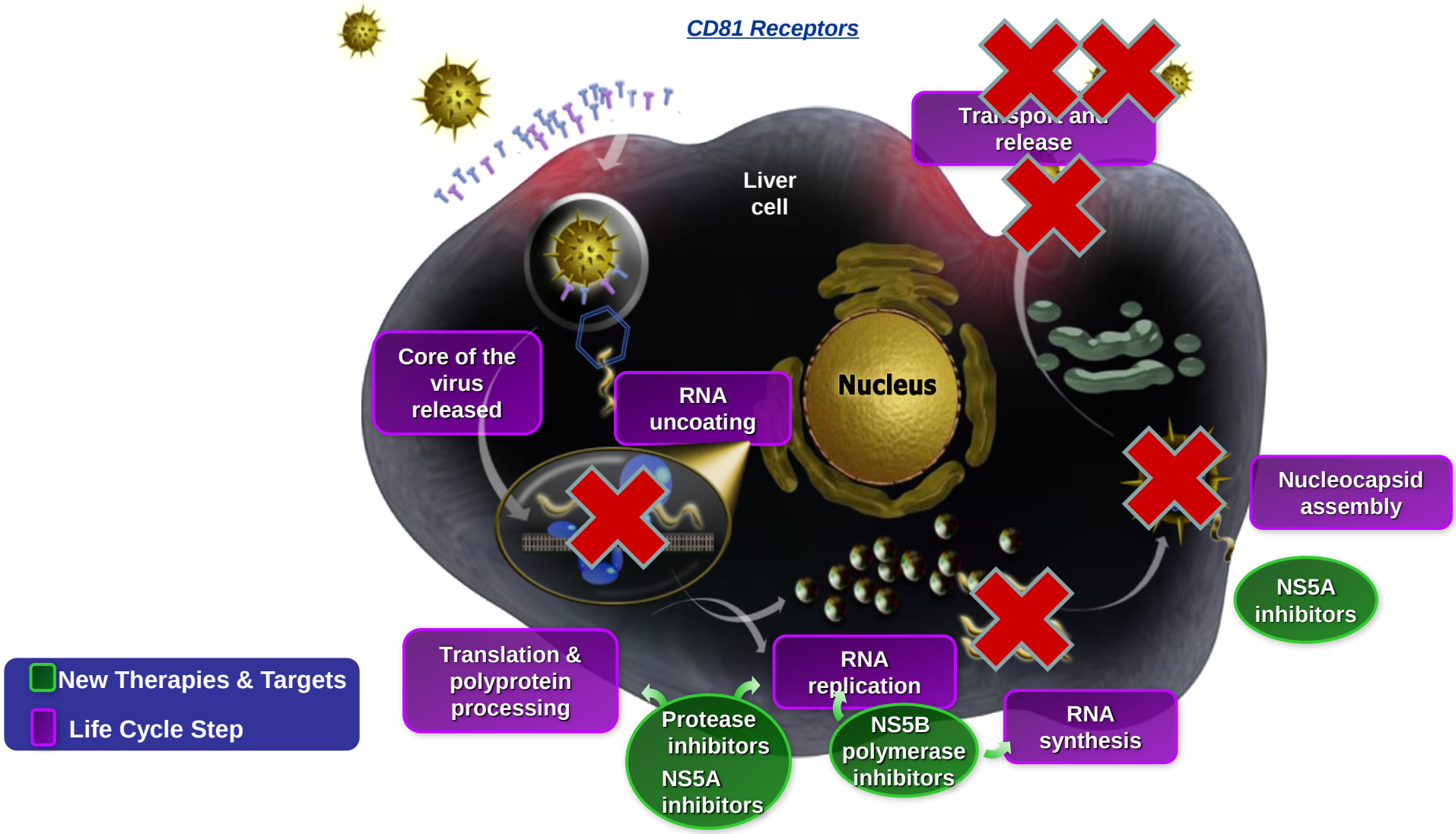


Cabibbo et al, DLD in press

Treatment of HCV Patients with Cirrhosis: Outline

- Indication to Treatment (Who to Treat?)
- Treatment recommendations (How to Treat?)

The HCV Life Cycle and Antiviral Therapy Targets



Combining DAAs to Maximize Efficacy

NS5B Polymerase Inhibitor

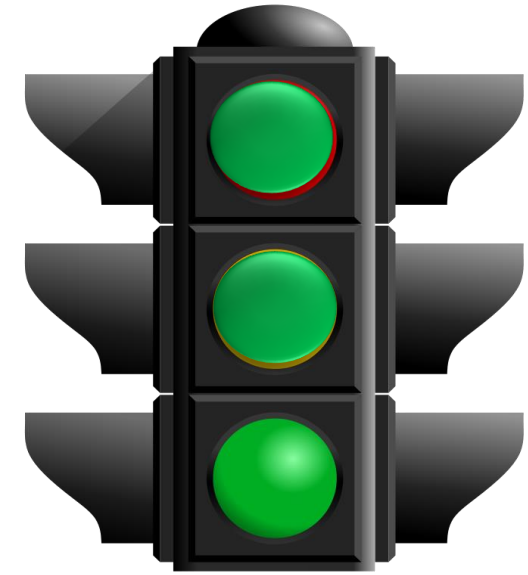
NS5A Inhibitors

Protease Inhibitors

Sofosbuvir + **Velpatasvir (NS5A)**

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

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



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§

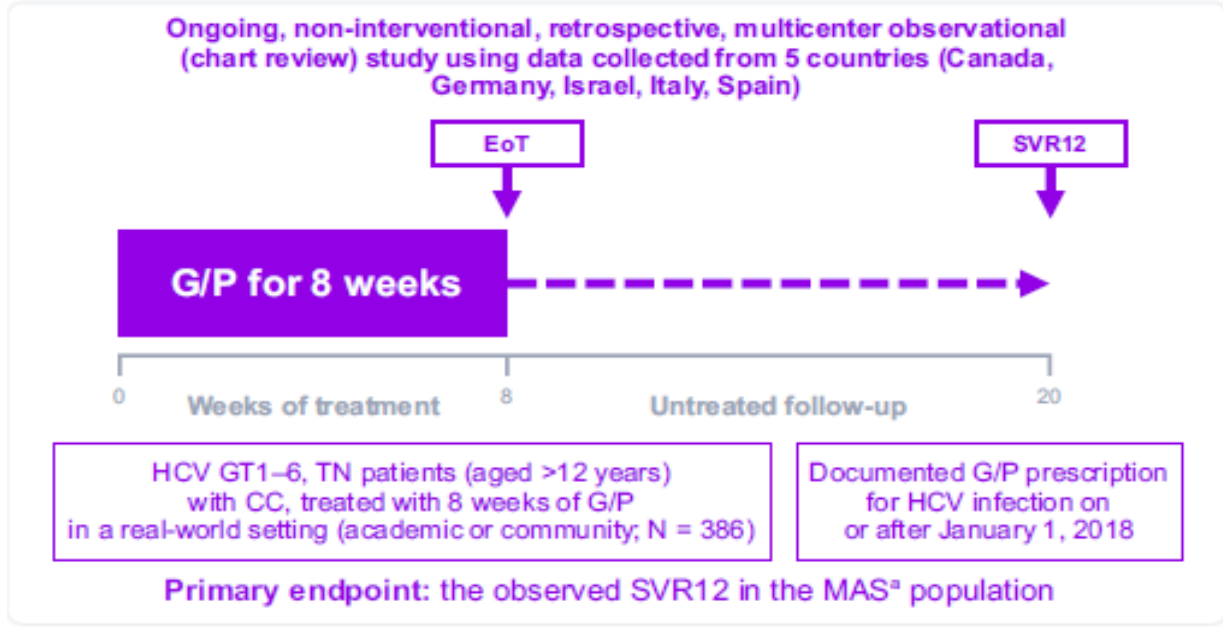
- *Child-Pugh A; †TE to pegIFN + RBV, pegIFN-α + RBV + SOF or SOF + RBV; ‡In TN patients infected with GT3 with CC, treatment with G/P can be shortened to 8 weeks, but more data are needed to consolidate this recommendation; § If resistance testing is formed, only patients with the NS5A Y93H RAS at baseline 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.

#942 Cornberg: Safety and Effectiveness Using 8 Weeks of Glecaprevir/Pibrentasvir in HCV-Infected Treatment-Naive Patients With Compensated Cirrhosis: The CREST Study

OBJECTIVE: To further corroborate registrational trial findings in real-world cohorts, this study investigated effectiveness and safety of 8-week G/P therapy in treatment-naive (TN) CC patients, with an emphasis on those with advanced liver disease (platelets <150,000/µL, FibroScan >20 kPa, or both platelets <150,000/µL and FibroScan >20 kPa) and patients with GT3 infection.

Figure 1. CREST Study Design



CC, compensated cirrhosis; EoT, end of treatment; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; MAS, modified analysis set; SVR12, sustained virologic response at post-treatment Week 12; TN, treatment naïve.

[a]MAS excludes patients who discontinue G/P for reasons other than virologic failure and/or who have missing data to document the primary endpoint.

#942 Cornberg: Safety and Effectiveness Using 8 Weeks of Glecaprevir/Pibrentasvir in HCV-Infected Treatment-Naive Patients With Compensated Cirrhosis: The CREST Study

Table 1. Demographics and Clinical Characteristics at Baseline

HCV RNA, median (Q1–Q3),[b] log_{10} IU/mL	6.1 (5.6–6.6)
Albumin, median (Q1–Q3),[c] g/dL	4.1 (3.8–4.4)
Bilirubin, median (Q1–Q3),[d] mg/dL	0.6 (0.5–0.9)
ALT, median (Q1–Q3),[e] IU/L	103.4 (46.0–278.8)
Platelets, median (Q1–Q3),[f] 10^3/µL	156.5 (17.5–512)
<150 × 10^3/µL, n/N (%)	166/363 (45.7)
<100 × 10^3/µL, n/N (%)	17/148 (11.5)
FibroScan, median (range),[g] kPa	13.6 (2.7–75.0)
>20 kPa, n/N (%)	45/335 (13.4)
≥12.5 kPa, n/N (%)	106/124 (85.4)
Platelets <150 × 10^3/µL and FibroScan >20 kPa, n (%)[h]	27 (8.2)
APRI score, median (range)[i]	2.0 (0.2–30.6)
FIB-4, median (range)[j]	3.8 (0.8–37.4)

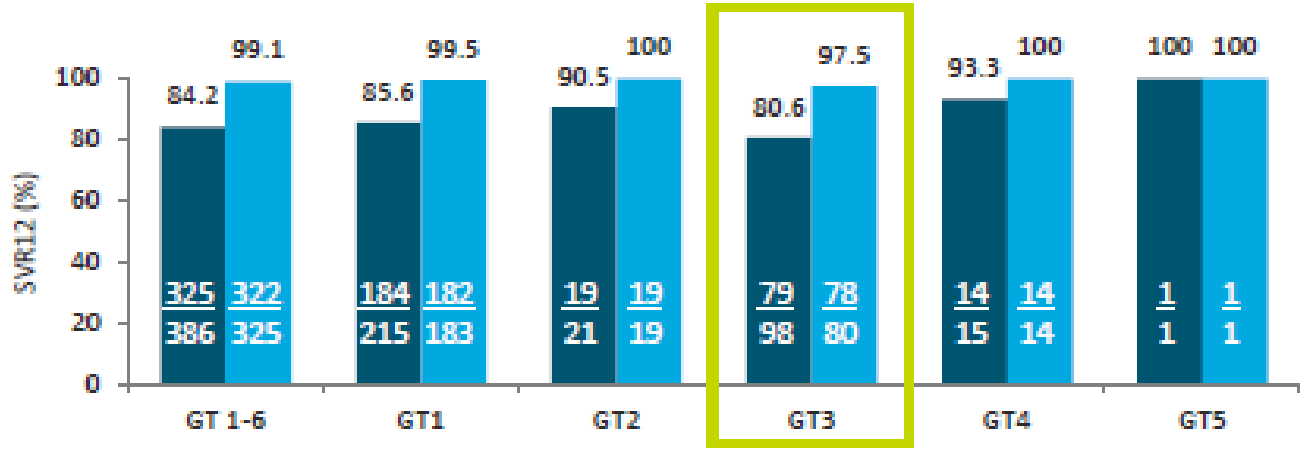
#942 Cornberg: Safety and Effectiveness Using 8 Weeks of Glecaprevir/Pibrentasvir in HCV-Infected Treatment-Naive Patients With Compensated Cirrhosis: The CREST Study

To corroborate trial findings in **real-world cohorts**, this chart review study investigated **effectiveness** and **safety** of 8-week G/P therapy in treatment-naive patients with chronic HCV

FAS: All patients

MAS: Excludes patients lost to follow-up and those discontinuing for reasons other than virologic failure

SVR by genotype

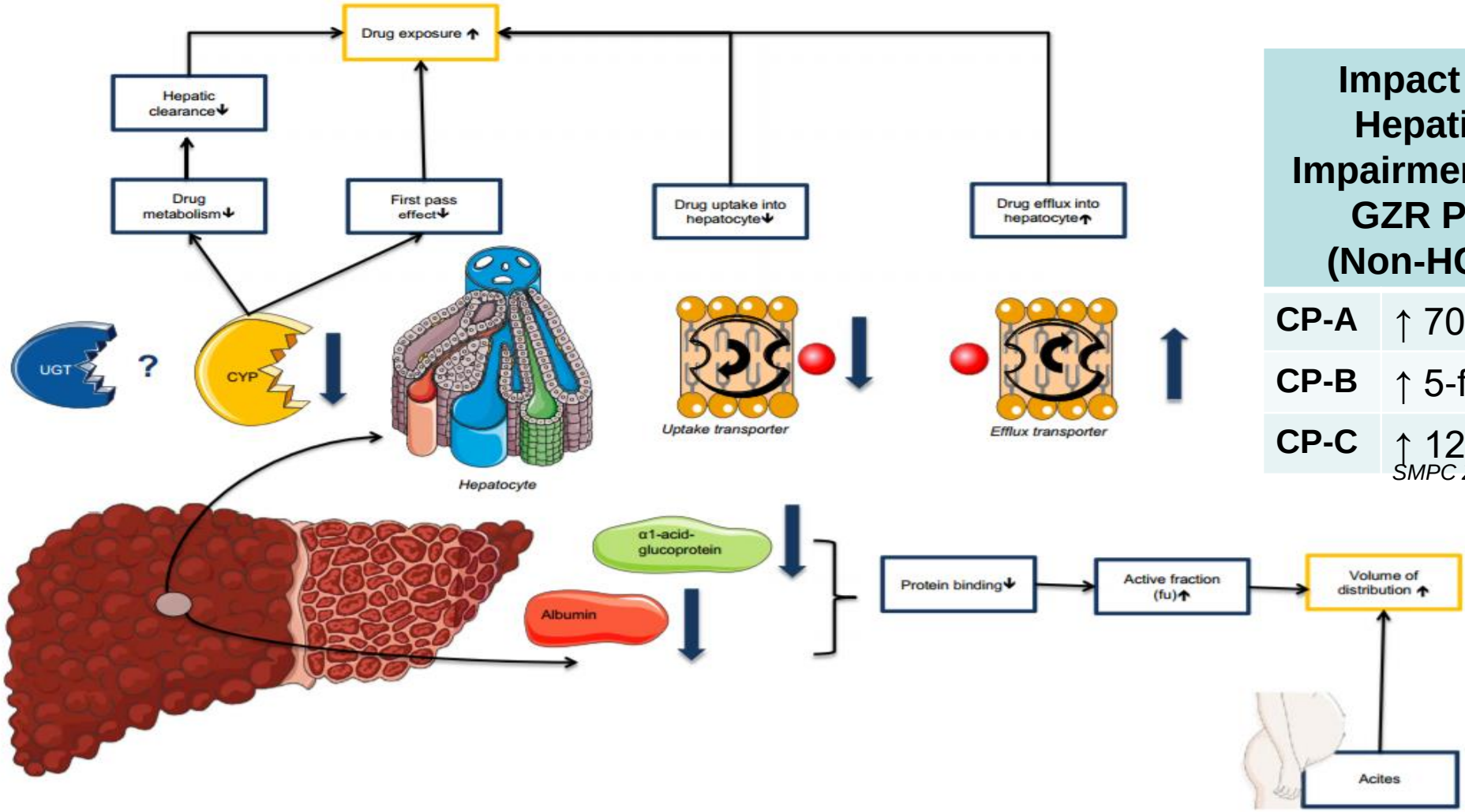


Safety

- 5 SAEs (1.3%; none related to study drug)
- Most common AEs (>5% of patients)
  - Fatigue (n=38, 9.8%)
  - Headache (n=24, 6.2%)

AE, adverse event; FAS, full analysis set; GT, genotype; MAS, modified analysis set; G/P, glecaprevir/pibrentasvir; PWID, people who inject drug; SAE, serious adverse event; SVR, sustained virologic response; SVR12, SVR at post-treatment Week 12.

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

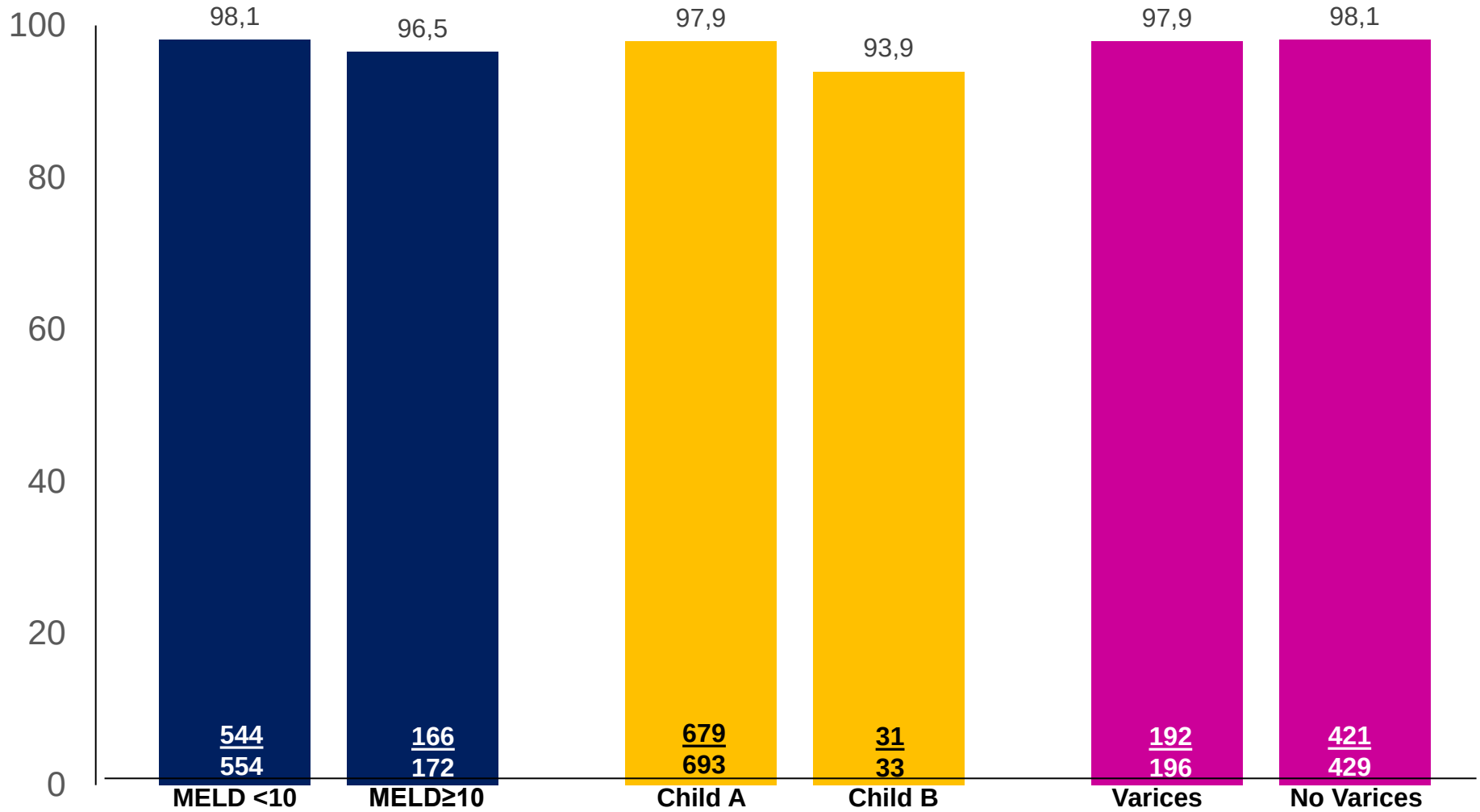
FDA Warning on the PrOD Regimen

«FDA Drug Safety Communication: FDA warns of serious liver injury with hepatitis C treatments Viekira Pak and Technivie»

«The U.S. Food and Drug Administration (FDA) is warning that hepatitis C treatments with Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, we are requiring the manufacturer to add new information about the safety risk to the drug labels […]. Some of these events resulted in liver transplantation or death. […] at least 26 worldwide cases submitted to FAERS were considered to be possibly or probably related to Viekira Pak or Technivie. In most of the cases, liver injury occurred within 1 to 4 weeks of starting treatment. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended […]»

FDA Drug Safety Communication; 22 October 2015

The ABACUS Study
Effect of Liver Function on SVR



Petta S et al, LGH 2017

Safety Analysis

11 Infectious Complications→ 3 in Child B
4 Hepatic Decompensation (2 variceal bleedings) → 1 in Child B

Discontinuation: 36
6 Child B

SVR 16/36

Breakthrough	2
Voluntary Interruption	3
Death	6
Adverse Events	25

Hyperbilirubinemia	3
Hepatic decompensation	2
HCC	1
Anemia	4
Infectious	3

Other	12

Safety Analysis: Death

Gender	Age	Child	Meld	Varices	Ascites	PLT<10000	Albumin <3.5	Time of Death	Cause of death
Female	68	B	13	1	1	No	Si	11 week	Pneumonia→ Hepatopulmonary Syndrome
Female	58	B	11	1	1	Si	Si	3 week	Cholecystitis→sepsis→MOF
Male	46	A5	10	1	0	Si	No	8 week	Car accident
Male	61	A5	10	1	0	-	No	4 month after stop therapy	Stop therapy after 4 weeks for bradicardia→ pace-maker→ after 3 months surgical resection of HCC→ AKI→ MOF
Male	48	A5	8	1	0	Si	No	14 week	Sudden death of unknown etiology
Female	66	A5	6	0	0	Si	No	FU week 4	Progression of lymphoma

Petta S et al, LGH 2017

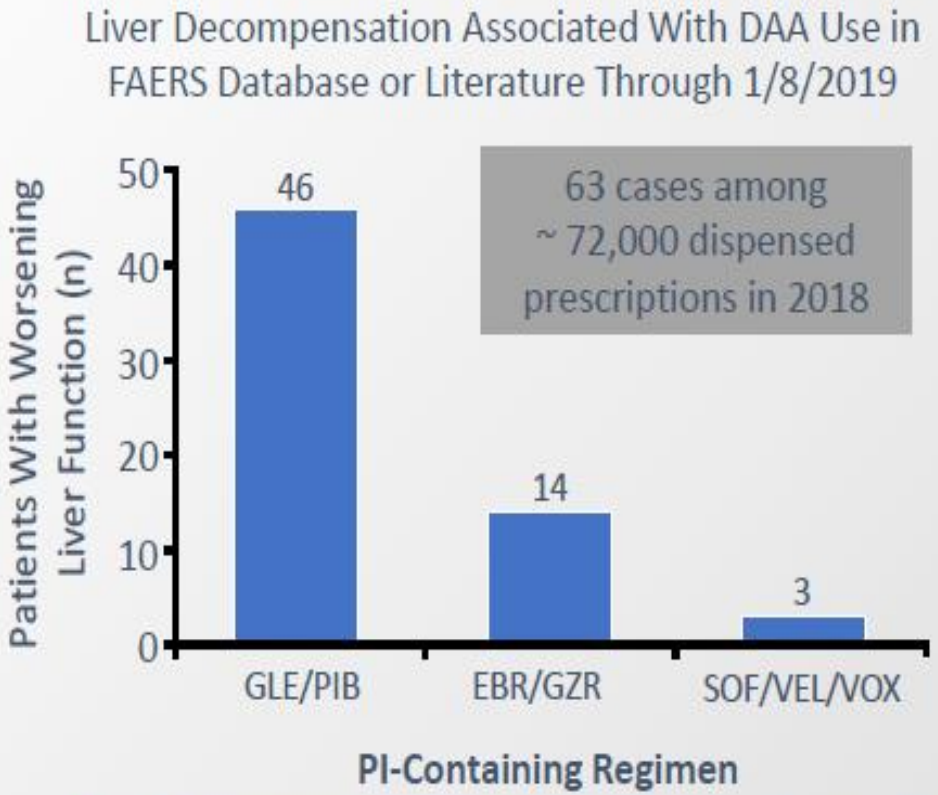
When are PIs Unsafe in Cirrhotic Patients?

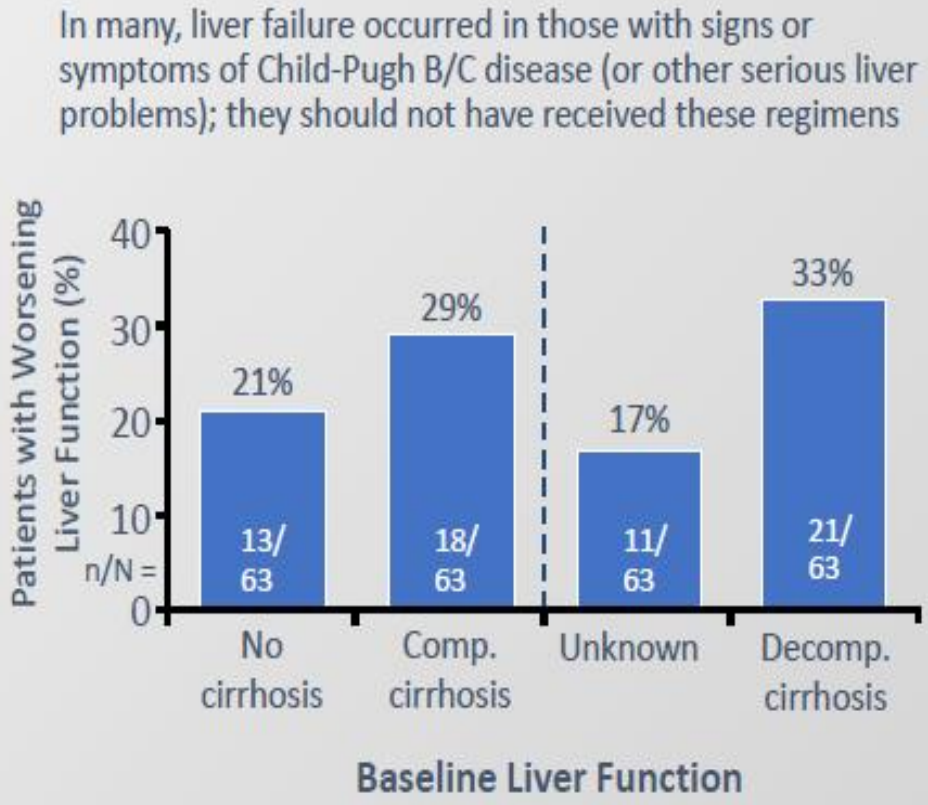
Characteristic	TEAE of interest*	
	No n = 1,053	Yes n = 13
Child-Pugh score, n (%)		
5	886 (86.2)	5 (38.5)
6	122 (11.9)	8 (61.5)†
>6	19 (1.8)	0
Missing or other	25	0

	Odds ratio [95% CI]	*p* value
Baseline albumin level (continuous, g/L)	0.85 [0.76, 0.96]	0.008
Baseline HCV RNA (continuous, $\log_{10}$ IU/ml)	0.39 [0.22, 0.72]	0.003
Prior history of non-selective beta blockers for varices (yes, no)	4.86 [1.19, 19.83]	0.028

Poordad F et al, J Hepatol 2017

Protease Inhibitors are Contraindicated in CPT B & C





Liver INTERNATIONAL

ORIGINAL ARTICLE

Real-world effectiveness and safety of direct-acting antivirals in patients with cirrhosis and history of hepatic decompensation: Epi-Ter2 Study

Aleksandra Berkan-Kawiń
Zdunek, Krzysztof Tomas
Iwona Buczyńska, Monika
Jakub Klapaczyński, Włod
Aleksander Garlicki, Mare
Białkowska-Warzecha, Ol
... See fewer authors

First published: 02 March

Liver INTERNATIONAL

RESEARCH LETTER

Sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus retreatment in decompensated cirrhosis

Sonalie Patel, Michelle T. Martin, Steven L. Flamm

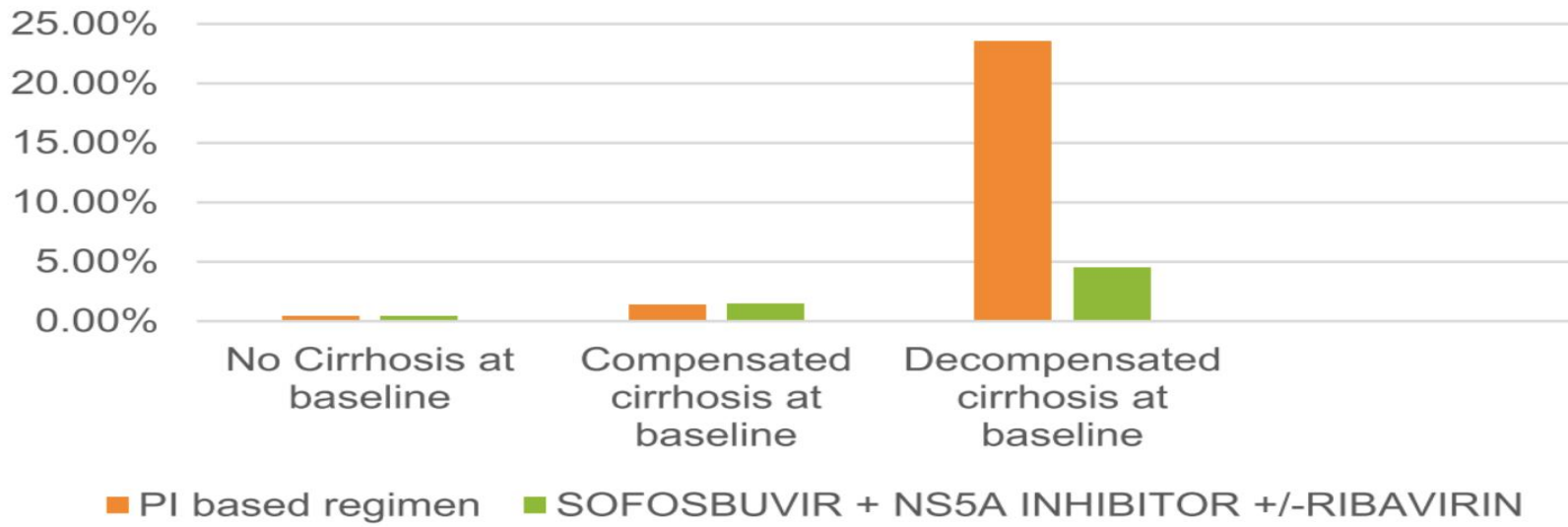
First published: 30 September 2021 | https://doi.org/10.1111/liv.15075

TABLE 1 Patient characteristics

Patient	1	2	3	4	5	6
Age (years)	82	63	57	56	62	52
Gender	Male	Male	Female	Male	Female	Male
BMI (kg/m^2)	30.6	22.5	29.2	37.6	29.3	34.3
Genotype/subtype	1b	3a	1a	1a	1a	3a
CTP Class (points)	B (8)	B (8)	B (7)	B (8)	B (9)	C (10)
Week 4						
HCV RNA (IU/ml)	Not detected	Not detected	126	Not detected	Not detected	Not detected
CTP CLass (points)	B (8)	B (7)	A (6)	B (7)	B (8)	B (7)
MELD-Na	15	14	11	10	15	16
Week 8						
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
CTP class (points)	B (8)	B (7)	A (6)	B (7)	B (7)	B (7)
MELD-Na	16	17	11	13	15	13
Week 12 (end of treatment)						
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
CTP class (points)	B (8)	B (7)	A (6)	B (7)	B (7)	B (7)
MELD-Na	17	13	12	12	14	17
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	886,538	Not detected	Not detected
CTP class (points)	B (7)	B (7)	A (5)	B (7)	B (7)	B (9)
MELD-Na	12	11	9	11	14	14

RESULTS

Prevalence of Hepatic Decompensation



A total of 55,930 patients were included of whom 36,053 used a PI based regimen (149 studies), and 19,877 used sofosbuvir + NS5A inhibitor +/- ribavirin (46 studies).

Among patients with no cirrhosis, the prevalence of decompensation on a PI containing regimen was 0.4%, 95% CI: 0.3-0.5%, I^2=0.00%, cases=14, studies= 82, and on a sofosbuvir/NS5A inhibitor regimen was 0.4%, 95% CI: 0.2-0.8%, I^2= 34.3%, cases=8, studies =25, respectively.

Among patients with compensated cirrhosis, decompensation events occurred on a PI regimen with prevalence = 1.4%, 95% CI: 1.1-1.7%, I^2= 17.2%, events= 116, studies= 59) and on a sofosbuvir/NS5A inhibitor regimen prevalence = 1.5%, 95% CI: 1.2-2.0, I^2=0.00%, cases =51, studies =14.

More patients with decompensated cirrhosis progressed on PI therapy, prevalence= 23.6%, 95% CI: 11.0-43.5%, I^2= 74.1%, events=37, studies =8 compared to a Sofosbuvir/NS5A inhibitor regimen with Prevalence= 4.5%, 95% CI: 3.2-6.2%, I^2= 19.5%, events=47, studies=7.

El Jamaly H et al, AASLD 2021