



Is the benefit to treat patients with cirrhosis proven?

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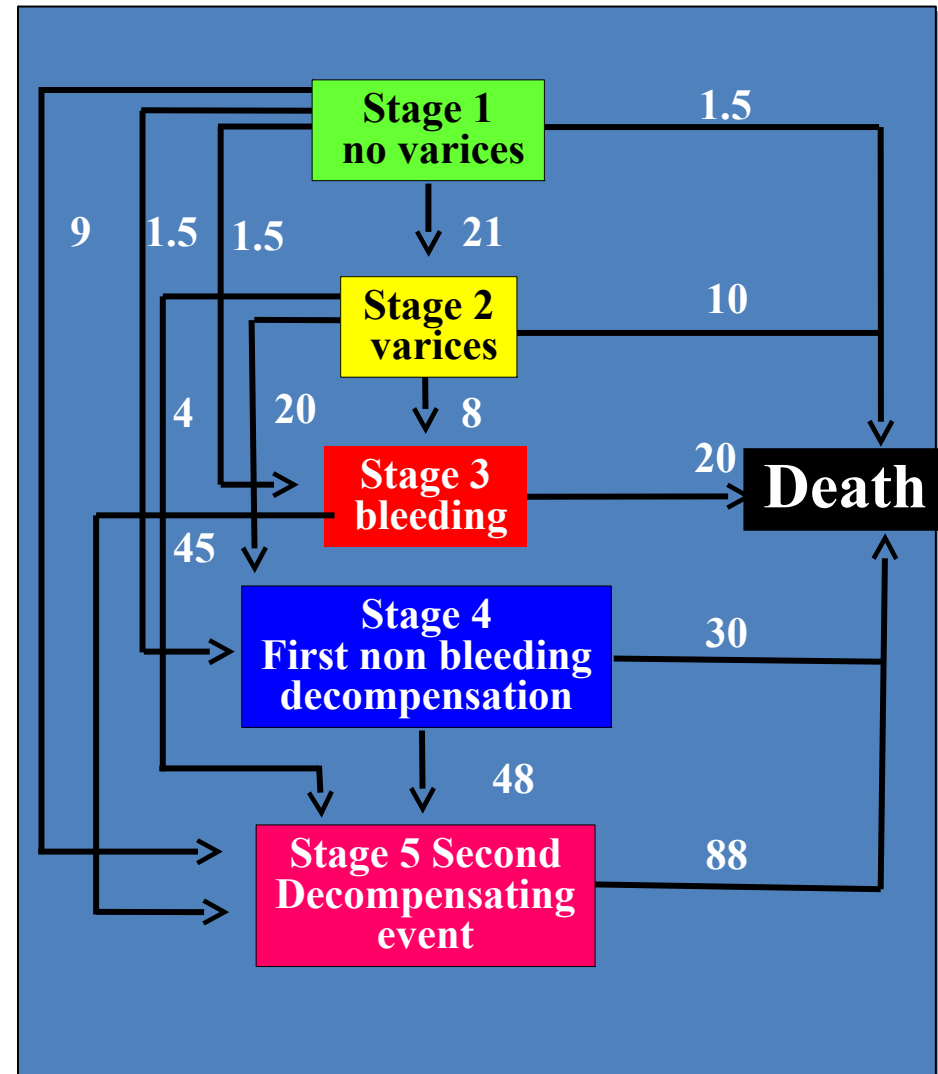
Humanitas University Medicine

Rozzano (Milan), Italy

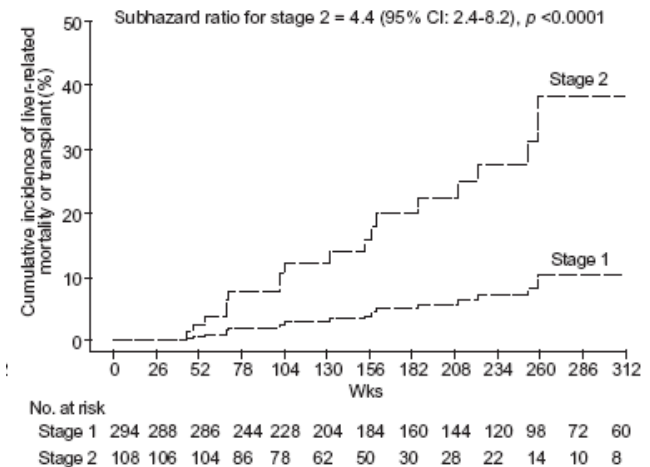
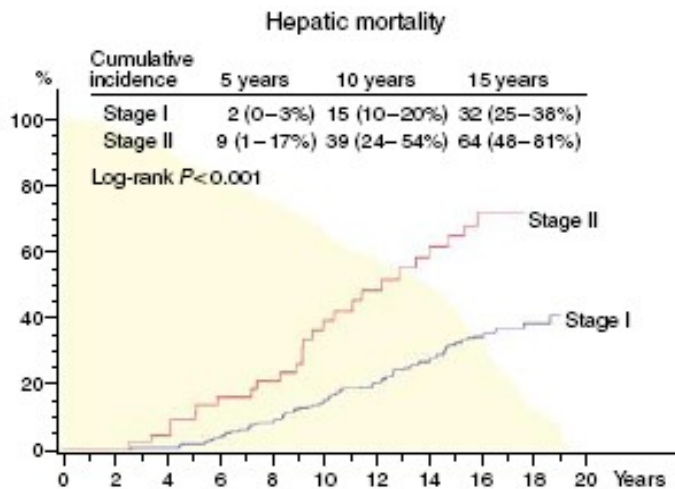
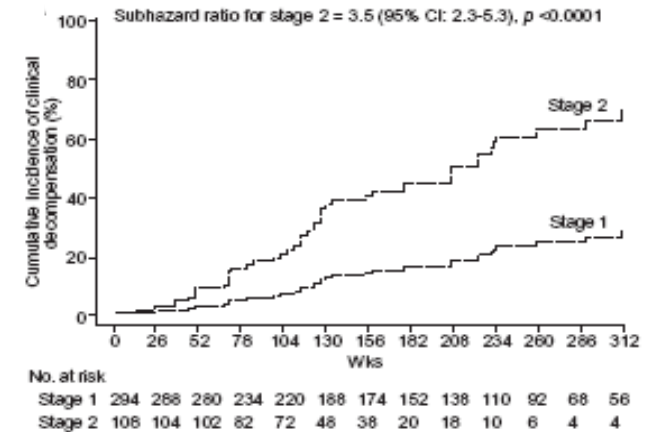
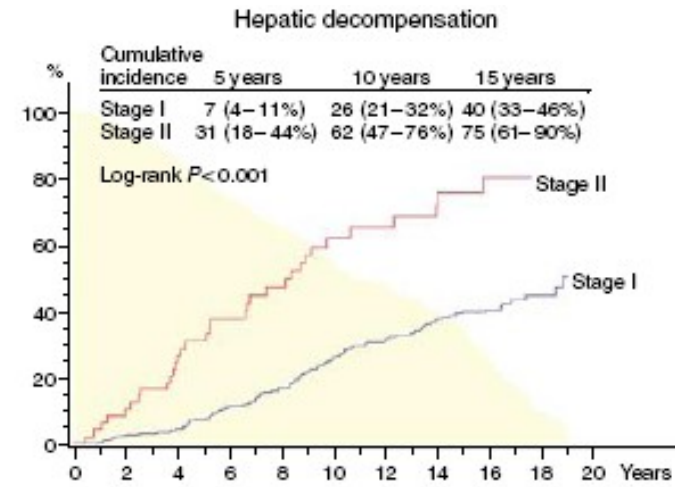


Multi-state Models to Improve Prognostic Scores

- Schematic representation of 5-year transitioning rates across stages and to death.
- Arrows represent transitions and the numbers represent transition rates
- Analysis for the risk of death showed that this multistate model provides incremental prognostic value to the MELD, together with age and HCC



Cumulative incidence of hepatic decompensation and hepatic mortality according to absence (stage 1) or presence (stage 2) of varices in 2 cohorts of HCV patients with compensated cirrhosis



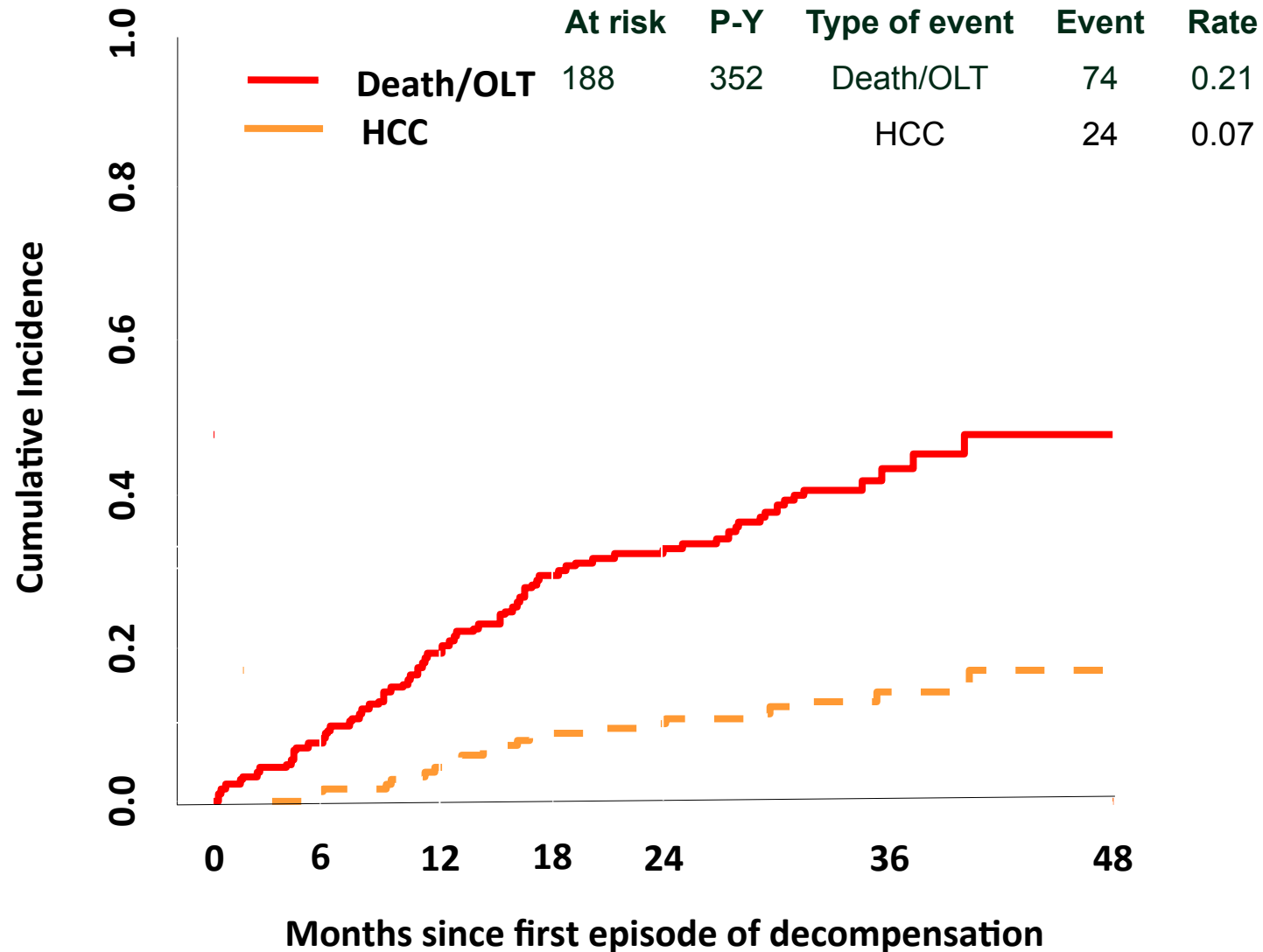
n= 352 patients

Bruno S, et al. Am J Gastroenterol 2009

n= 402 patients

Gomez EV, et al. J Hepatol 2013

**Liver – related mortality/OLT since first episode of decompensation.
A three-years prospective study**



HCV-related compensated cirrhosis:

a condition with a wide heterogeneity of clinical, biochemical and histological features at different prognosis

F2 Metavir, F2 to 3 Ishak, LSM ≥ 6 Kpa < 9.5 Kpa (possible overlap with either less or more severe stage), APRI <0.5 (possible overlap)

ADVANCED FIBROSIS stage

(F3 Metavir, F3 to 4 Ishak, LSM ≥ 9.5 Kpa < 12.5 Kpa (possible overlap with either less or more severe stage), APRI >0.5 <1.5 (possible overlap))

WELL COMPENSATED cirrhosis

F4 Metavir, F5 to 6 Ishak or LSM ≥ 12.5 or 14,3 KPa#, usually no clinically significant portal hypertension*: HVPG ranging between 6, and 10 mmHg, no esophageal varices, **Child A5, MELD < 10**

MARGINALLY COMPENSATED cirrhosis

LSM: ≥ 20 KPa#, with moderate to severe portal hypertension§: HVPG ≥ 12 mmHg, ±esophageal varices, PLT $\leq 100000/\text{mm}^3$, albumin value < 35gr/dl, **Child A6, MELD ≥ 10**

DECOMPENSATED

Child B7 to C12. MELD >15. waiting for OLT

#Castera L. Gastroenterology 2012

*Garcia Tsao G. et al, Hepatology 2010

§Qamar A. et al, Hepatology 2008

Baveno VI Consensus

New Concept: Compensated Advanced Chronic Liver Disease (cACLD)

The introduction of non invasive methods to
diagnose fibrosis has allowed the early
identification of patients with chronic liver
disease at risk of developing clinically significant
portal hypertension.

Does a biological plausibility exist in considering SVR a reliable surrogate marker of disease outcome?

Rates of cirrhosis regression in HCV patients who achieved SVR to IFN-based therapy

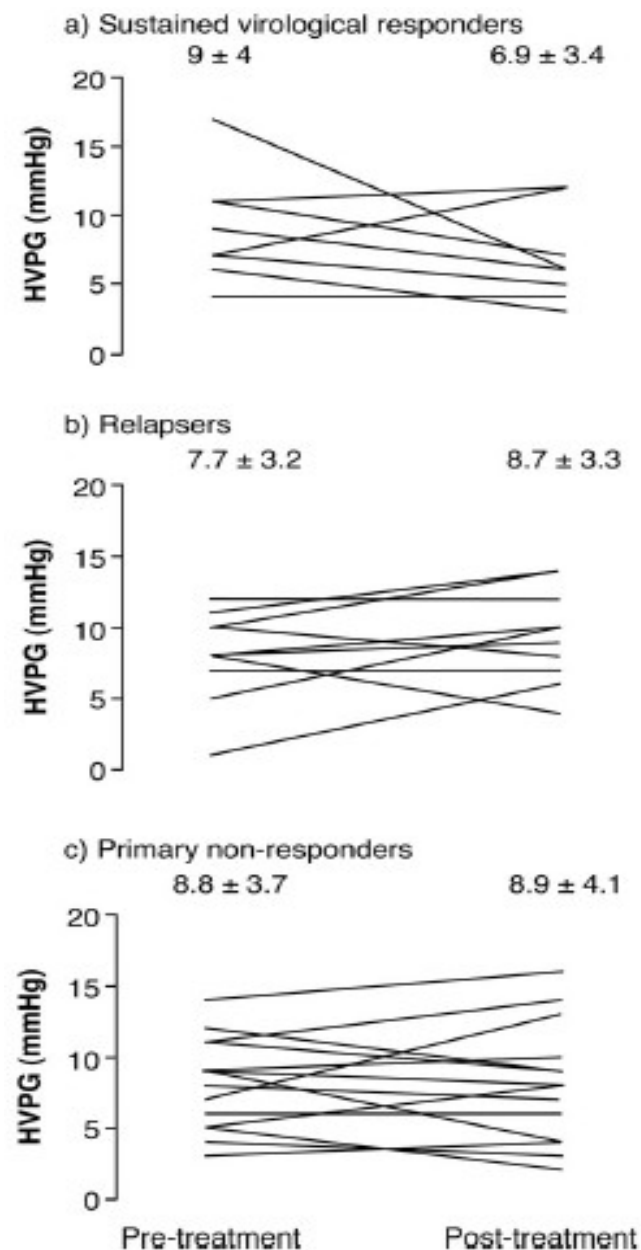
| Study | Patients with cirrhosis (n) | Months from SVR | Staging system | Regression rates (n/%) |
|------------------------|-----------------------------|-----------------|----------------|------------------------|
| Reichard et al. 1999 | 3 | 24-96 | Scheuer | 3 (100%) |
| Arif et al. 2003 | 6 | 6-72 | Ishak | 5 (83%) |
| George et al. 2009 | 8 | 56 | Ishak | 6 (75%) |
| Poynard et al. 2002 | 37 | <24 | Metavir | 25 (68%) |
| D'Ambrosio et al. 2012 | 38 | 48-104 | Metavir | 23 (61%) |
| Everson et al. 2008 | 40 | 6 | Metavir | 20 (50%) |
| Shiratori et al. 2000 | 24 | 12-120 | Metavir | 11 (46%) |
| Mallet et al. 2008 | 39 | 11 | Metavir | 17 (44%) |
| Pol et al. 2004 | 17 | NA | Metavir | 4 (24%) |
| Maylin et al. 2008 | 14 | 6 | Metavir | 9 (64%) |

Effect of Treatment on HVPg According to Virologic Response

| Parameter | Virologic response | | P value |
|------------------------------------|--------------------------|--------------------------|---------|
| | Sustained viral response | Nonresponse ^a | |
| HVPg, mm Hg | | | |
| Pretreatment | 9.0 ± 4.0 | 8.0 ± 3.1 | NS |
| Posttreatment | 6.9 ± 3.4 | 8.6 ± 3.7 | NS |
| Change in HVPg, mm Hg | -2.1 ± 4.6 | 0.6 ± 2.8 | .05 |
| ≥20% decrease in HVPg ^b | 5/7 (71%) | 4/20 (20%) | .01 |

^aIncludes primary nonresponders and relapsers.

^bIncludes only subjects with baseline HVPg of greater than 5 mm Hg.



Impact of SVR on the development of esophageal varices

SVR prevents de-novo development of esophageal varices in compensated HCV cirrhosis

218 Pts

Untreated
n= 69

Treated
n= 149

Median
follow-up:

11,4 years

7,5 years

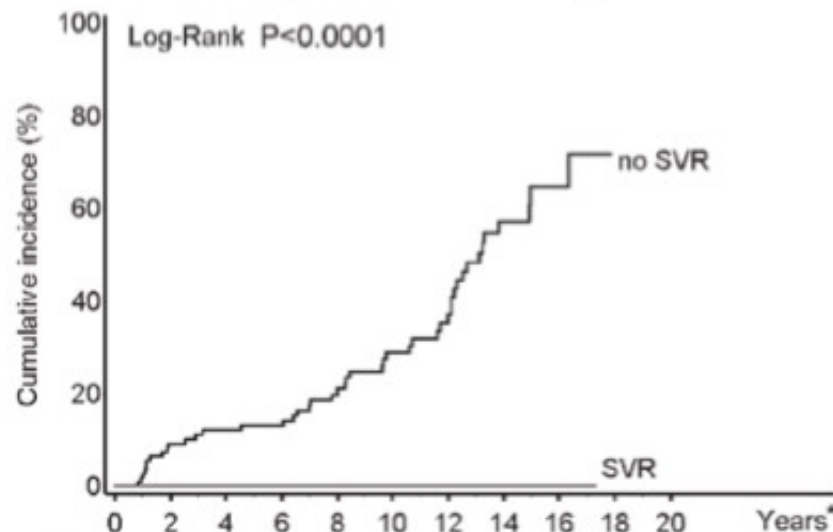
Varices (n)

21

Varices (%)

30,4

Response to antiviral therapy

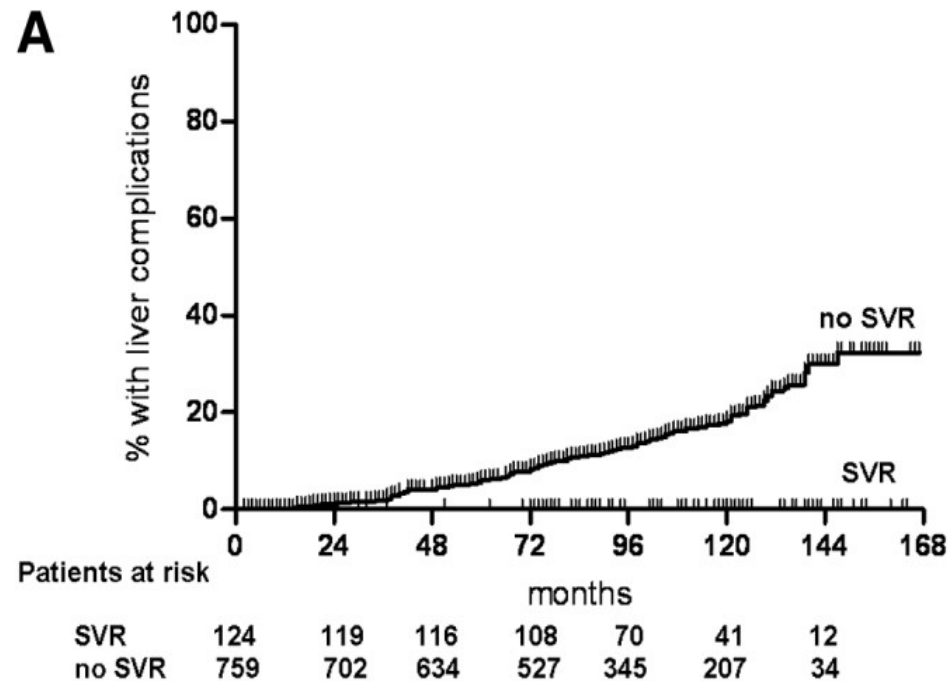


Patients at risk

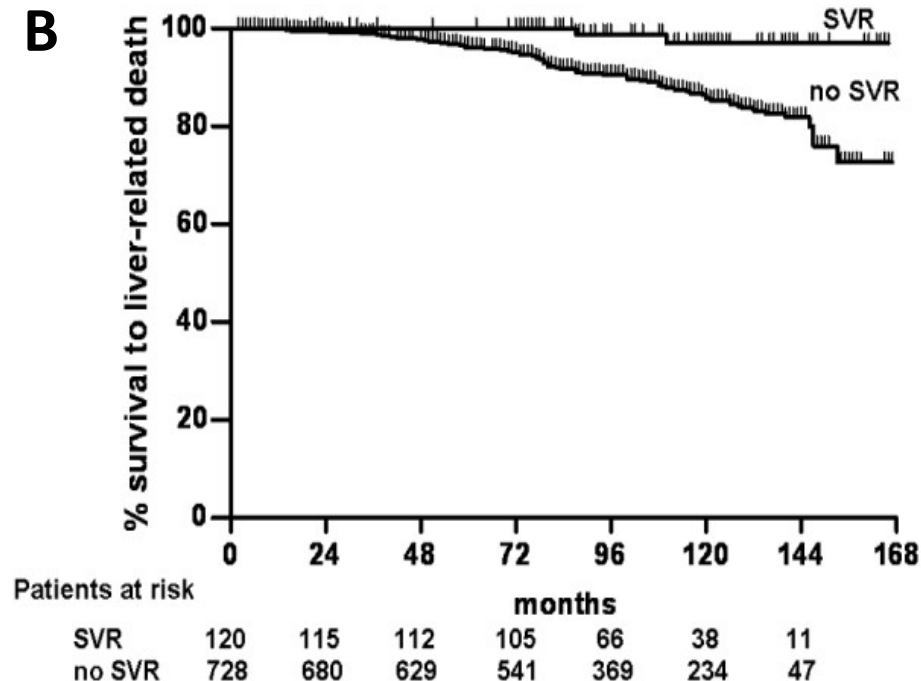
| | | | | | | |
|--------|-----|----|----|----|---|---|
| No SVR | 115 | 89 | 65 | 35 | 7 | 0 |
| SVR | 34 | 30 | 27 | 17 | 7 | 0 |

*since antiviral treatment initiation

Cumulative incidence of liver-related complications (A) and liver-related mortality (B) in patients with HCV-related histologically proven cirrhosis stratified according to response to IFN ($P=0.001$ by log-rank test)

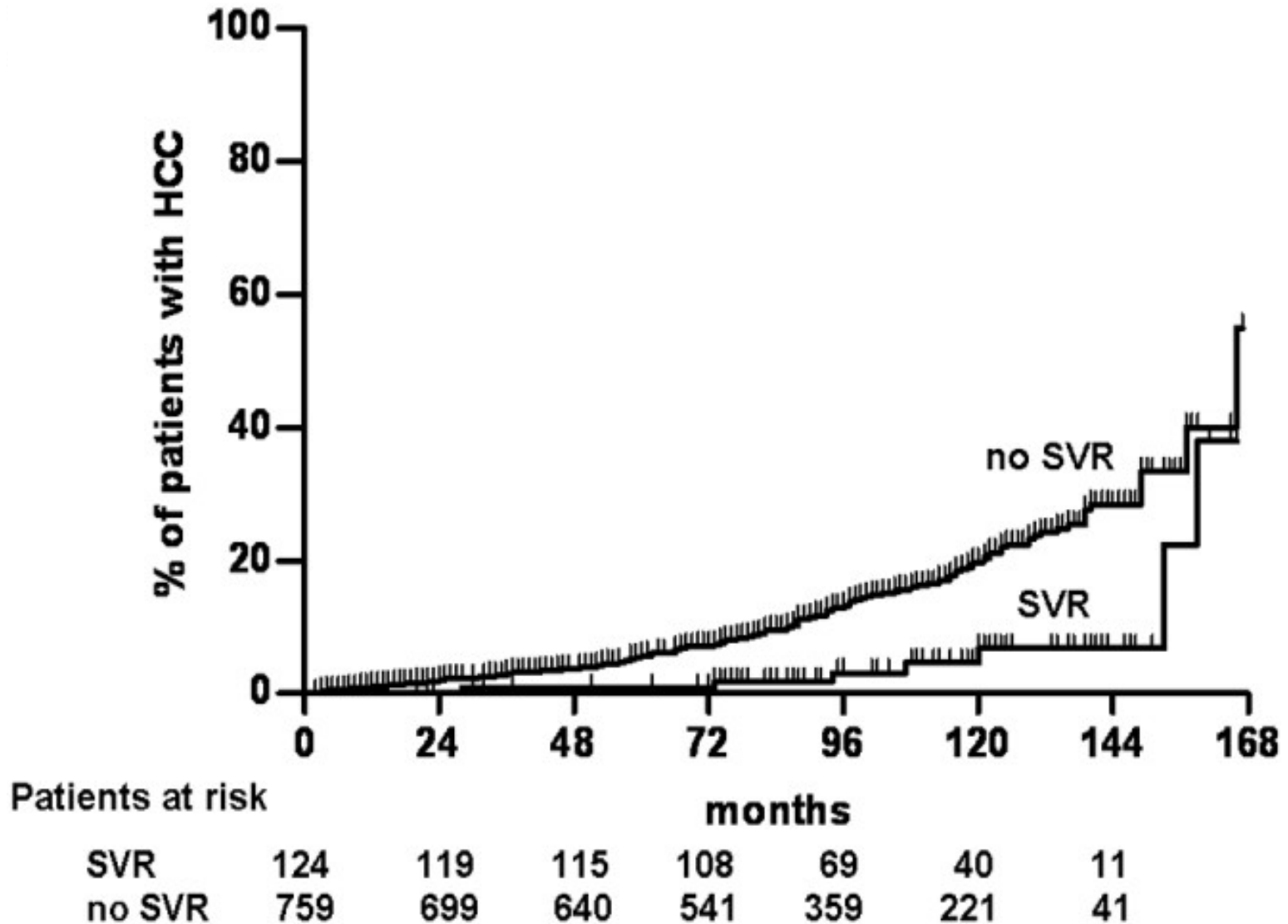


883 patients

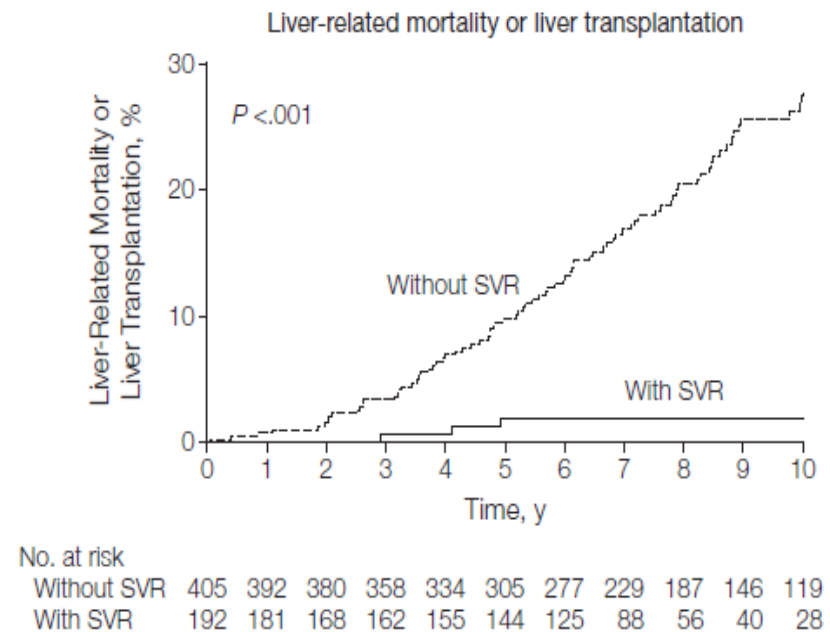
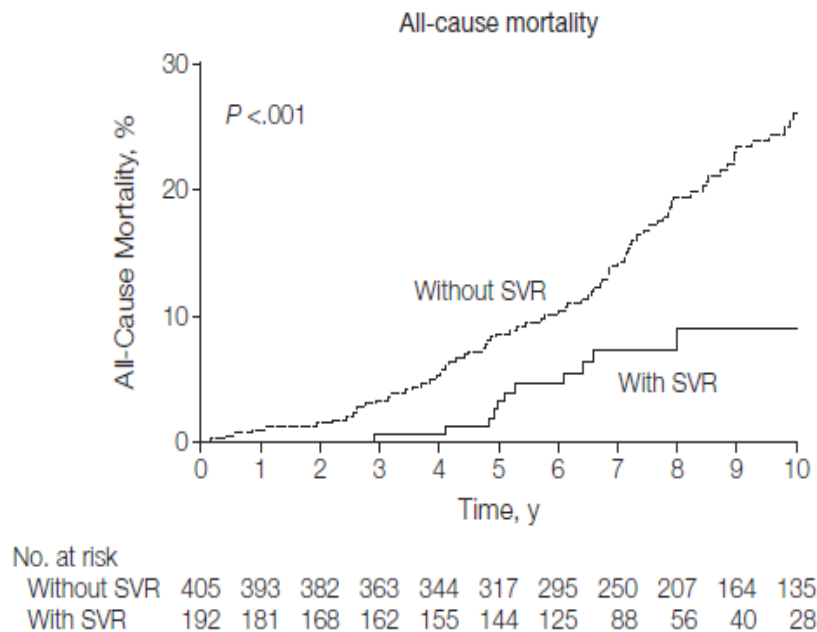


848 patients: patients died for non-liver-related causes were excluded

Cumulative incidence of HCC in 883 patients with HCV-related histologically proven cirrhosis stratified according to response to IFN (P=0.001 by log-rank test)



Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV

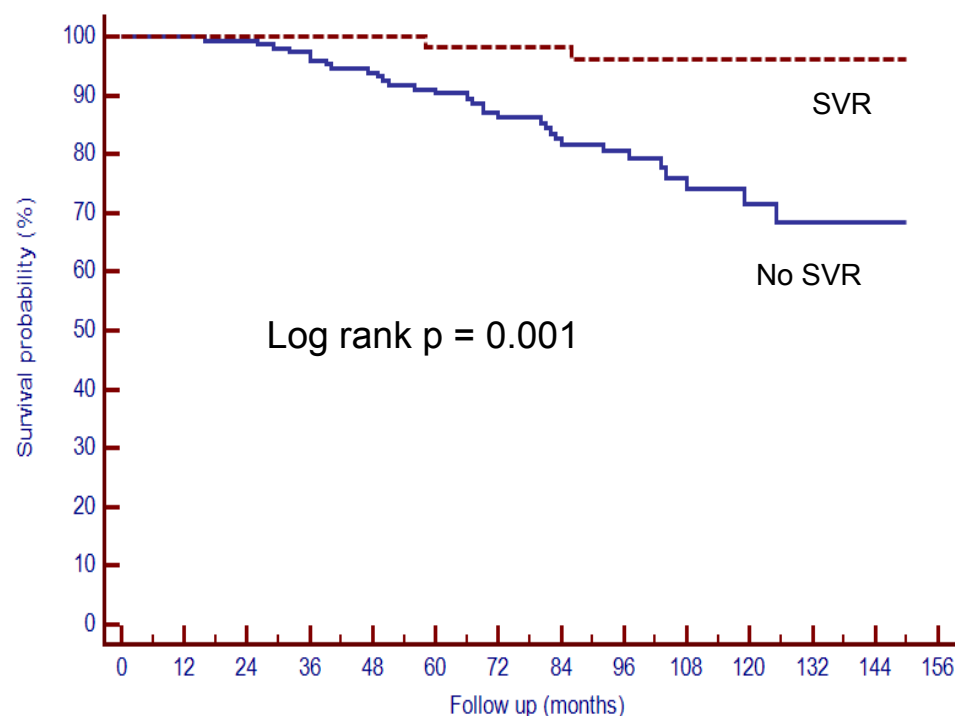


Survival after P/R treatment in 440 patients with HCV cirrhosis, C-P A5-6 (mean follow-up time 7.7

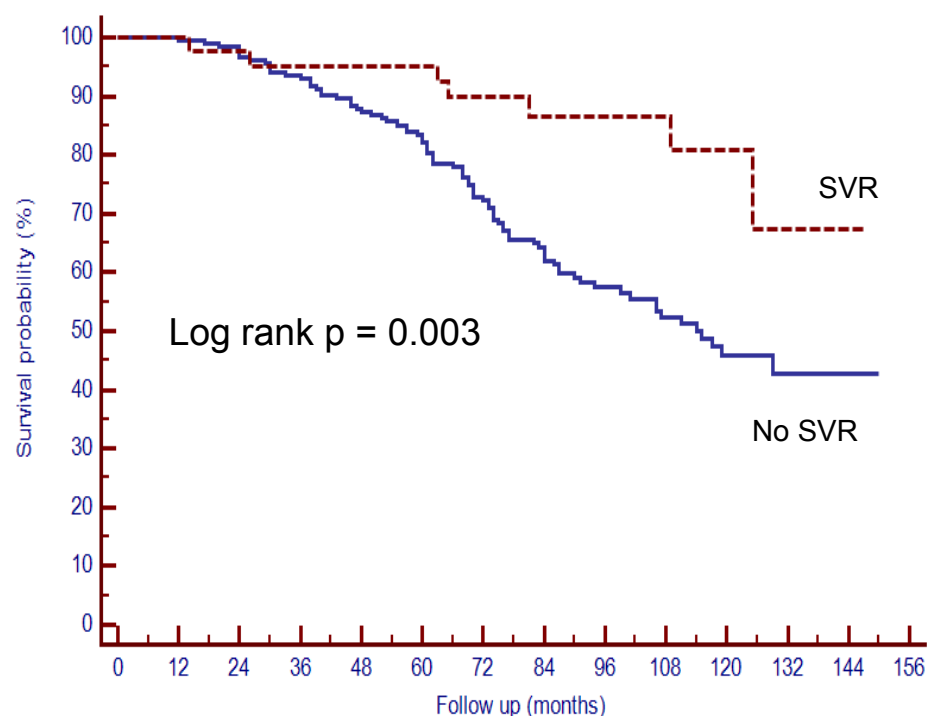
yrs)

No esophageal varices (Stage1)
before P/R

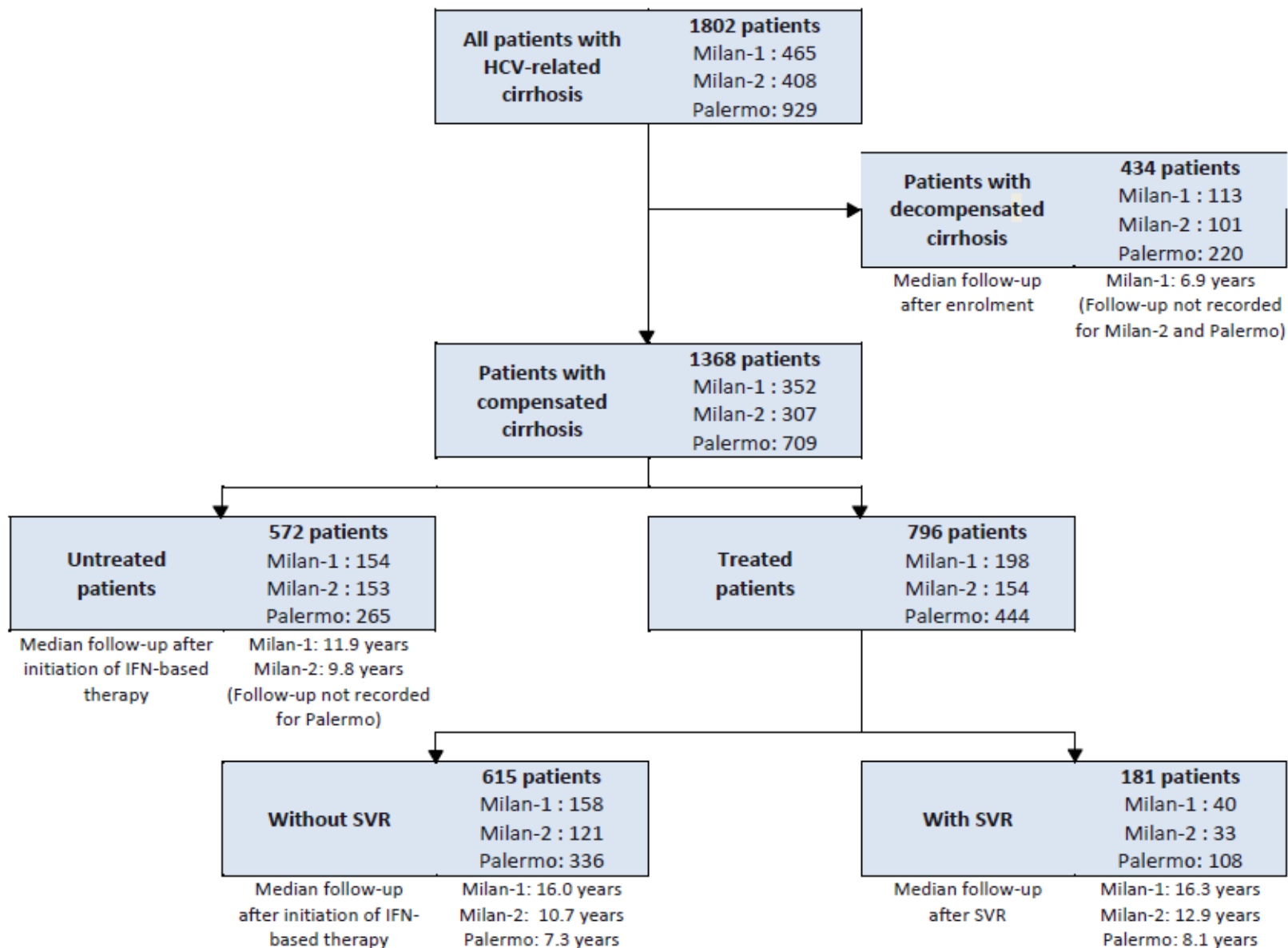
Esophageal varices (Stage2)
before P/R



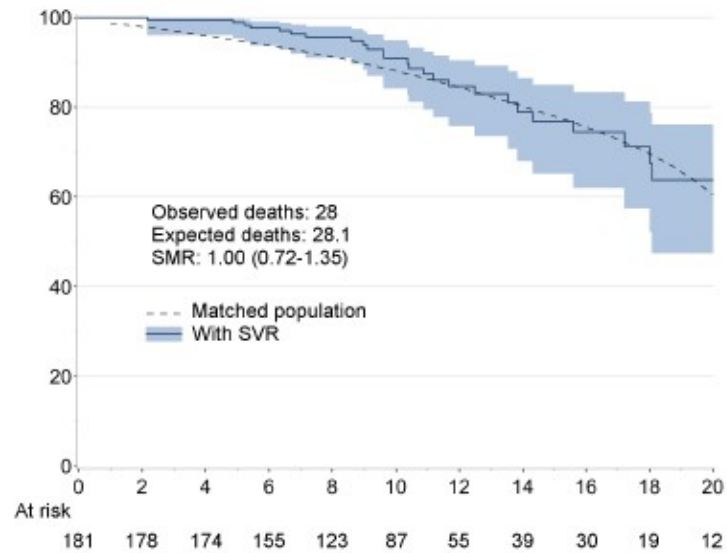
| | | | | | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|---|--|
| Number at risk | | | | | | | | | | | | | | |
| Group: No SVR | | | | | | | | | | | | | | |
| 148 | 148 | 147 | 141 | 135 | 121 | 104 | 86 | 61 | 40 | 25 | 15 | 5 | 0 | |
| Group: SVR | | | | | | | | | | | | | | |
| 67 | 67 | 67 | 67 | 65 | 56 | 51 | 44 | 30 | 20 | 16 | 8 | 2 | 0 | |



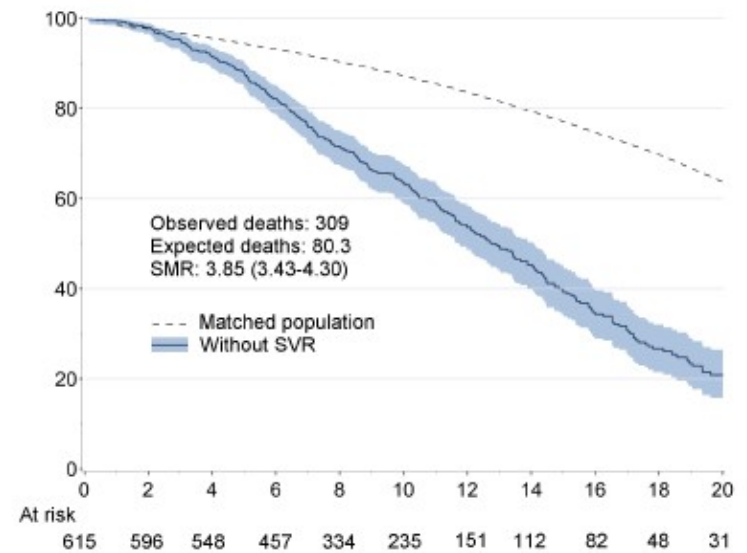
| | | | | | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|----|----|----|----|---|---|---|--|
| Number at risk | | | | | | | | | | | | | | |
| Group: No SVR | | | | | | | | | | | | | | |
| 184 | 183 | 177 | 168 | 156 | 137 | 111 | 85 | 67 | 49 | 26 | 9 | 1 | 0 | |
| Group: SVR | | | | | | | | | | | | | | |
| 41 | 41 | 40 | 39 | 37 | 36 | 32 | 26 | 22 | 15 | 8 | 3 | 1 | 0 | |



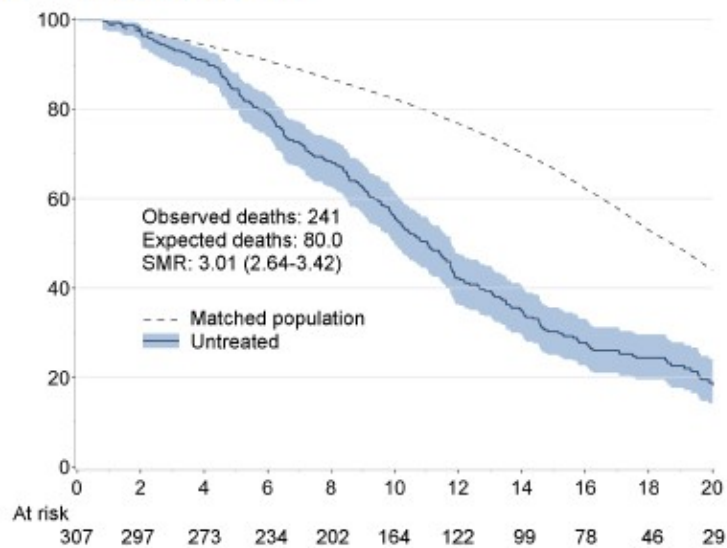
A Patients with SVR



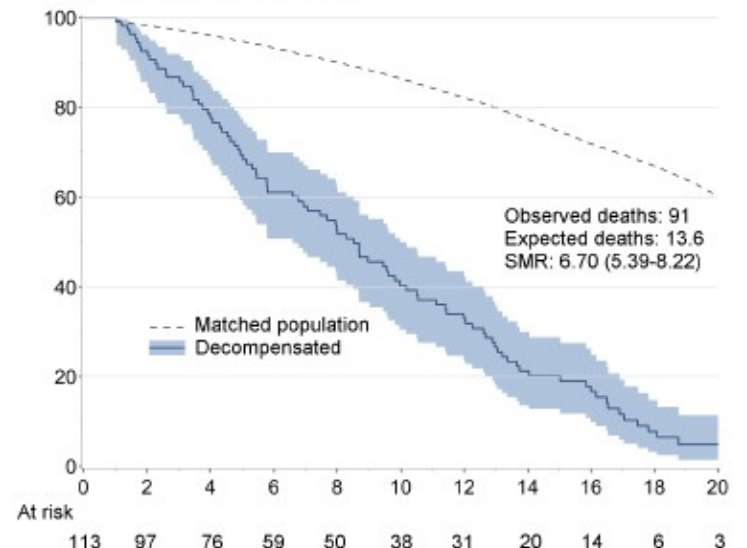
C Patients without SVR



B Untreated patients



D Decompensated patients



Multivariate analysis of predictors of outcome in patients with SVR

| | Overall mortality (28 deaths) | | Liver related deaths (18 events*) | | Hepatic decompensation (11 events) | | Hepatocellular carcinoma (20 Cases) | |
|---------------------------|----------------------------------|--------------|--------------------------------------|--------------|---------------------------------------|-------------------|--|--------------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age | | | | | | | | |
| 55-59 vs. <55 years | 2.63 (0.67-10.3) | 0.22 | | | | | 2.52 (0.49-12.9) | 0.27 |
| 60-64 vs. <55 years | 5.54 (1.57-19.5) | 0.008 | | | | | 3.64 (0.72-18.3) | 0.12 |
| ≥65 vs. <55 years | 3.80 (0.88-13.4) | 0.07 | | | | | 4.85 (0.92-25.7) | 0.06 |
| Gender | | | | | | | | |
| men vs. women | | | 6.80 (1.51-30.6) | 0.01 | | | | |
| Alfa-fetoprotein | | | | | | | | |
| ≥10 ng/mL vs. <10 ng/mL | | | | | | | 7.19 (2.06-25.1) | 0.002 |
| Albumin | | | | | | | | |
| ≤3.5 g/dL vs. >3.5 g/dL | | | 4.32 (1.12-16.7) | 0.03 | 10.7 (2.35-48.8) | 0.002 | | |
| Platelets | | | | | | | | |
| <80,000/mL vs. ≥80,000/mL | 2.94 (1.24-9.92) | 0.01 | 4.47 (1.59-12.6) | 0.005 | 28.2 (5.85-136.) | <0.0001 | | |

Hazards Ratio (HR) and 95% confidence intervals (CI) obtained from stepwise Cox proportional hazards regression models. All factors that did not satisfy the criteria (Pr Chi-square <0.10) to stay in the model in were removed in a step down phase.

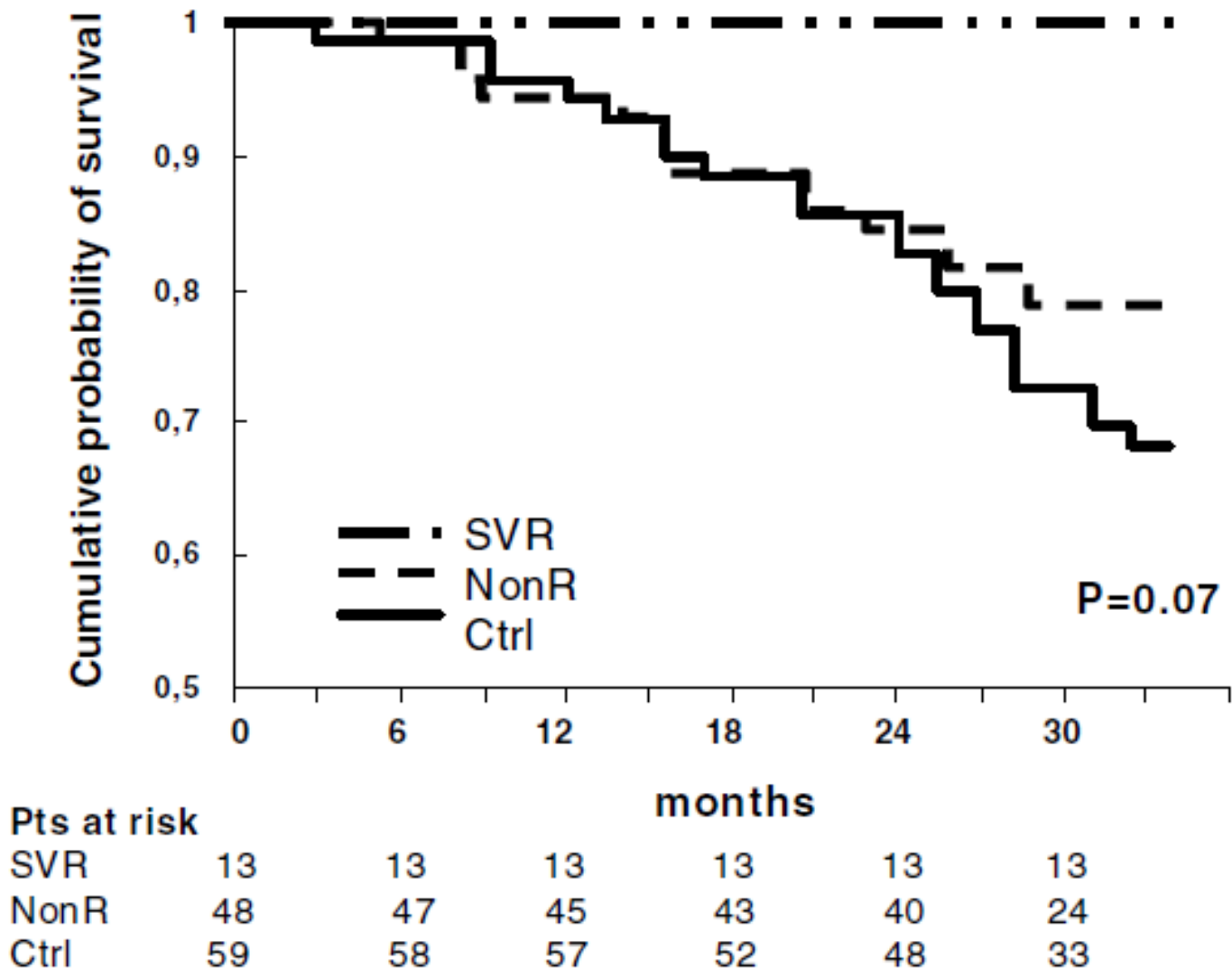
* Including 4 OLTs

IFN –BASED Tx in Decompensated Cirrhosis

| | | | HCV-RNA Neg | |
|---------------|------------|---------|-------------|------------|
| Author | N | Rx | EOT | SVR |
| Iacobellis | 66 | Peg/RBV | 49% | 20% |
| Forns | 51 | Peg/RBV | 29% | 20% |
| Tekin | 20 | Peg/RBV | 45% | 30% |
| Annichiarico | 15 | Peg/RBV | 47% | 20% |
| | | | | |
| Everson | 124 | IFN/RBV | 46% | 24% |
| Forns | 30 | IFN/RBV | 30% | 20% |
| Thomas | 20 | IFN | 60% | 20% |
| Amarapukar | 18 | IFN/RBV | 61% | 38% |
| Crippin | 15 | IFN/RBV | 33% | 0% |
| | | | | |
| TOTALS | 359 | | 44% | 24% |

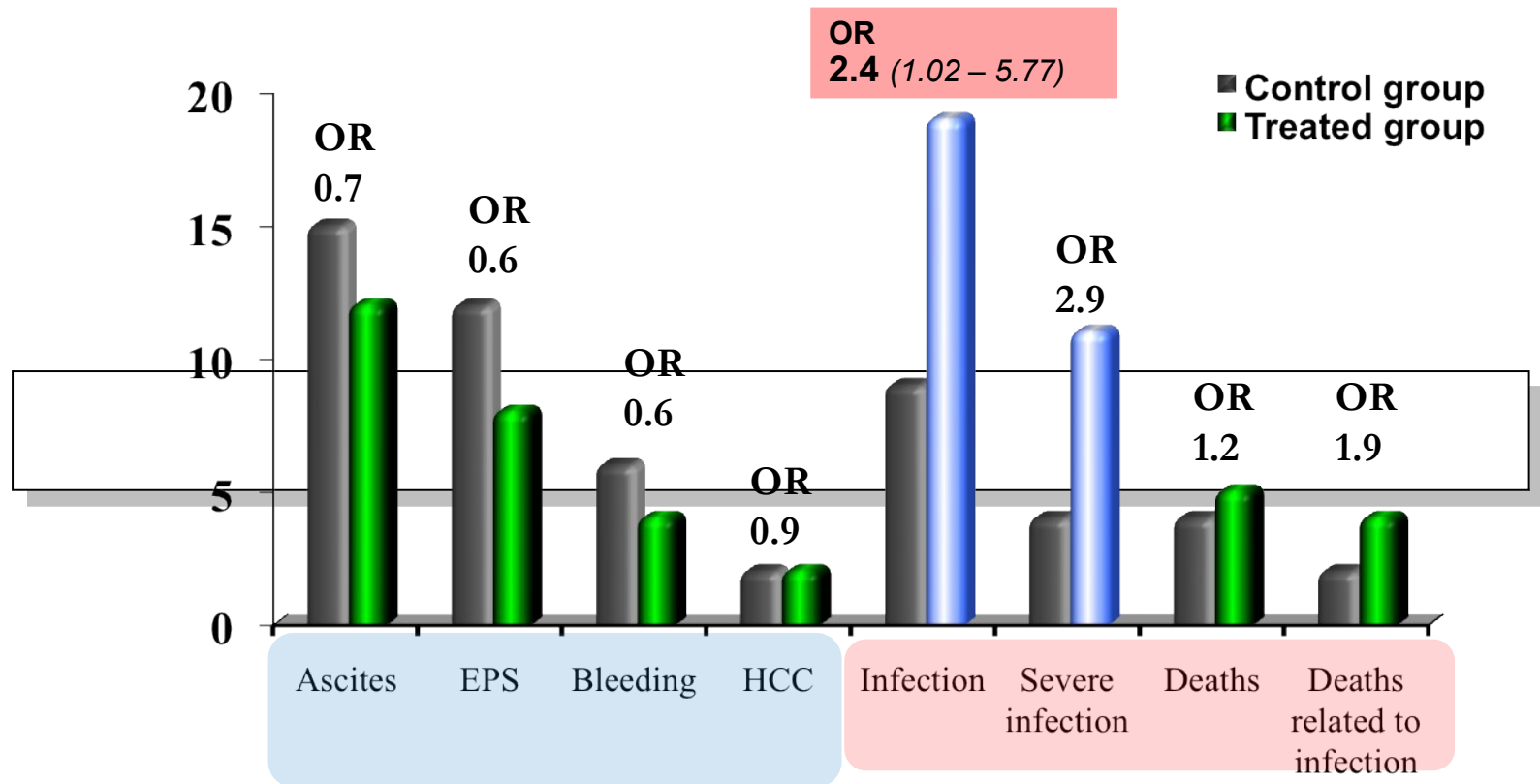
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Chronic Hepatitis C: Advances in Treatment, Promise for the Future. ML Shiffman (ed). 2012.
 In
 Springer Science-Business. NY.

Cumulative survival after IFN –BASED treatment in patients with decompensated cirrhosis



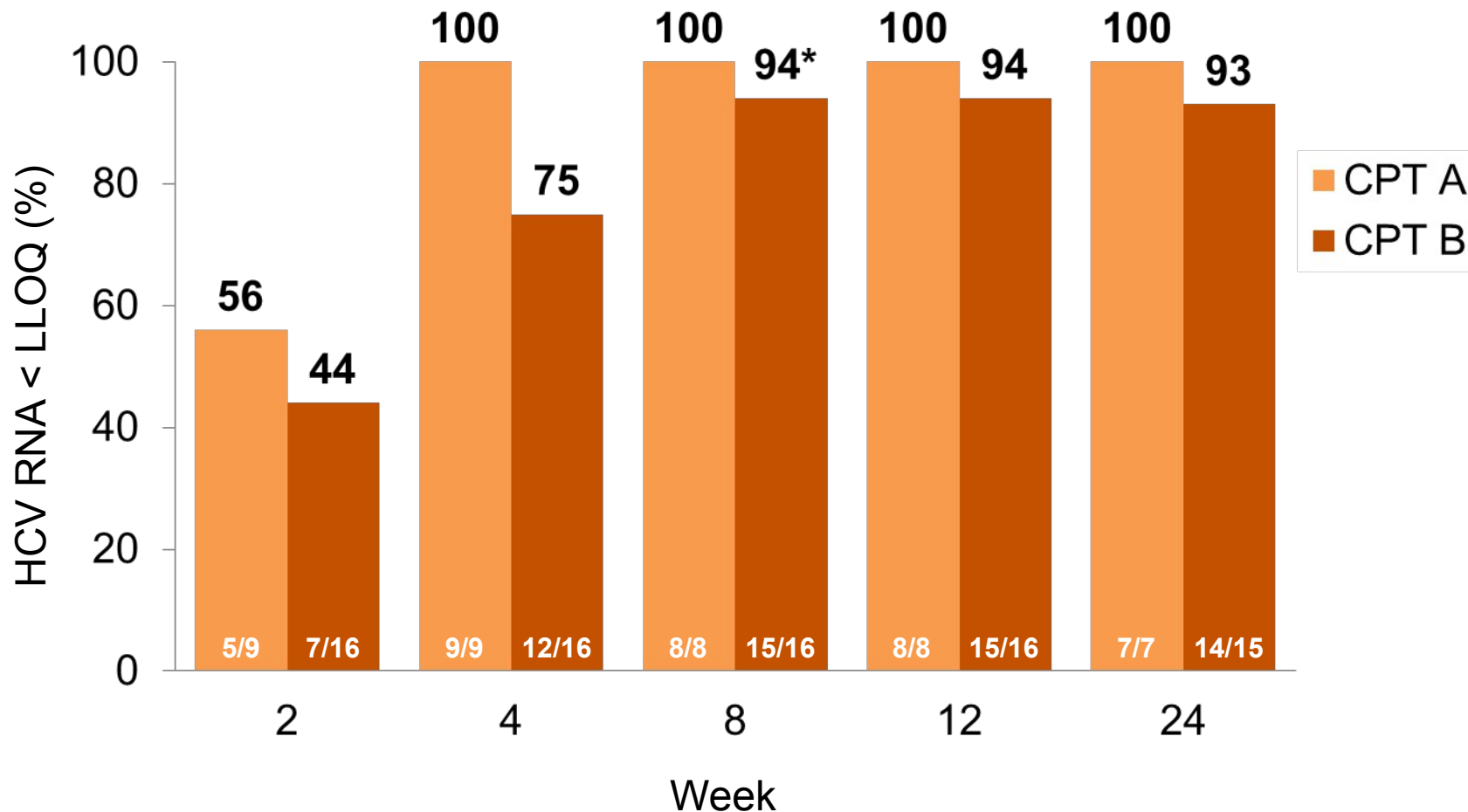
Safety and tolerability

Deaths and AEs in the first 6 months of follow-up according to treatment or not



Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension \pm decompensation

On Treatment Virologic Response



*1 patient was a non-responder at Week 8.

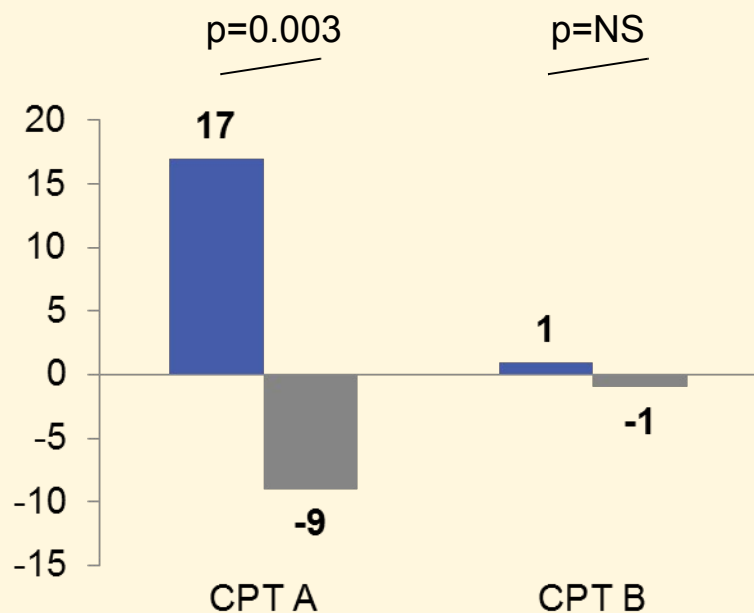
Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension \pm decompensation

Laboratory Results: Mean Changes from Baseline to Week 24

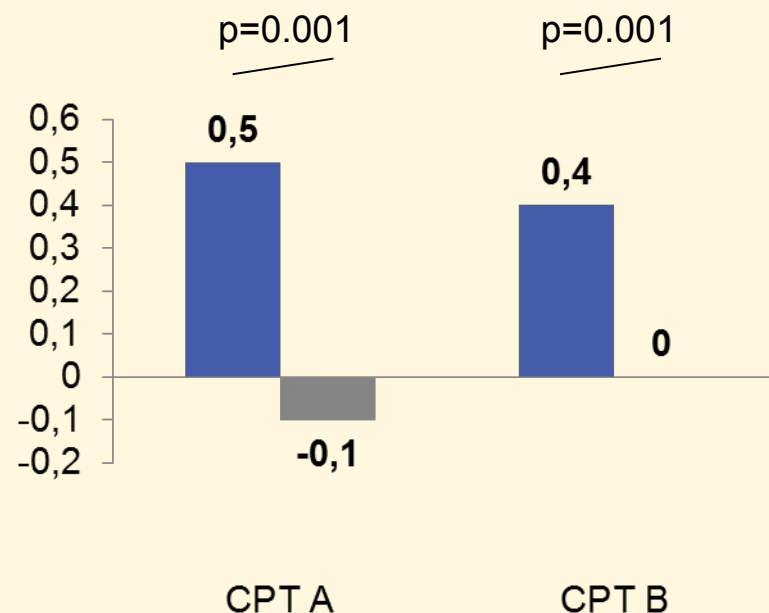
■ SOF+RBV

■ Observation 24 weeks

Platelets (103/ μ L)



Albumin (g/dL)



- ◆ Changes in PT/INR were not observed in either CPT A or B patients with treatment or observation

Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension \pm decompensation

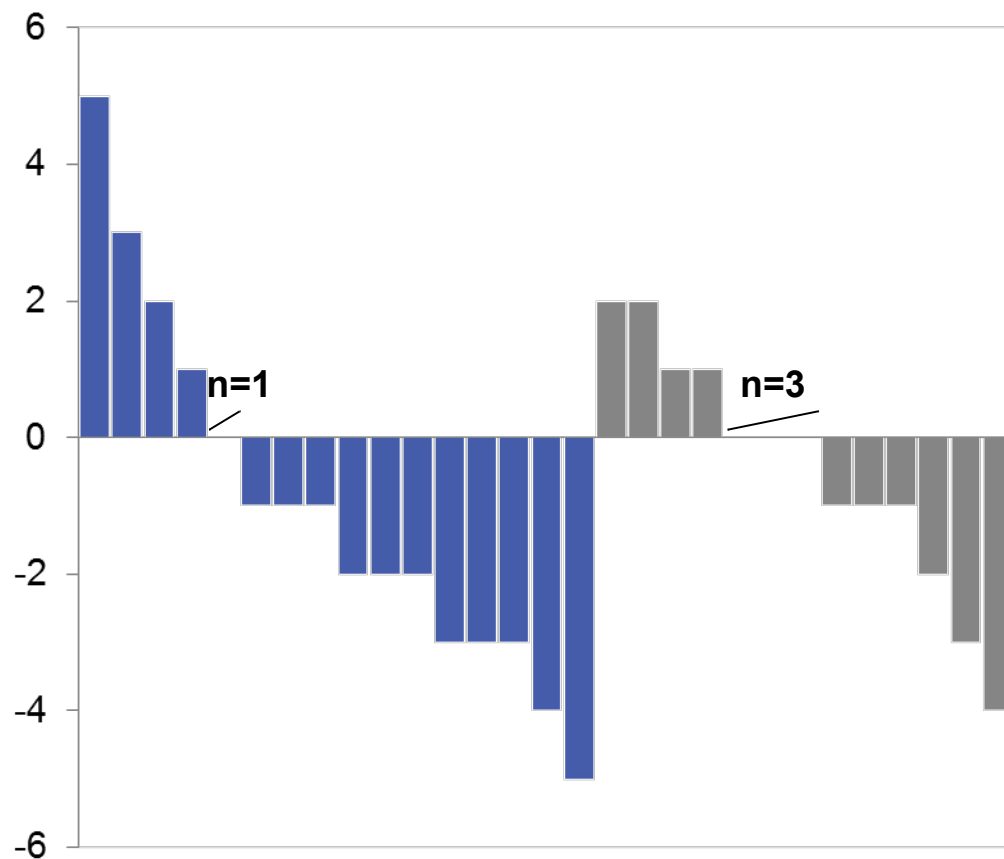
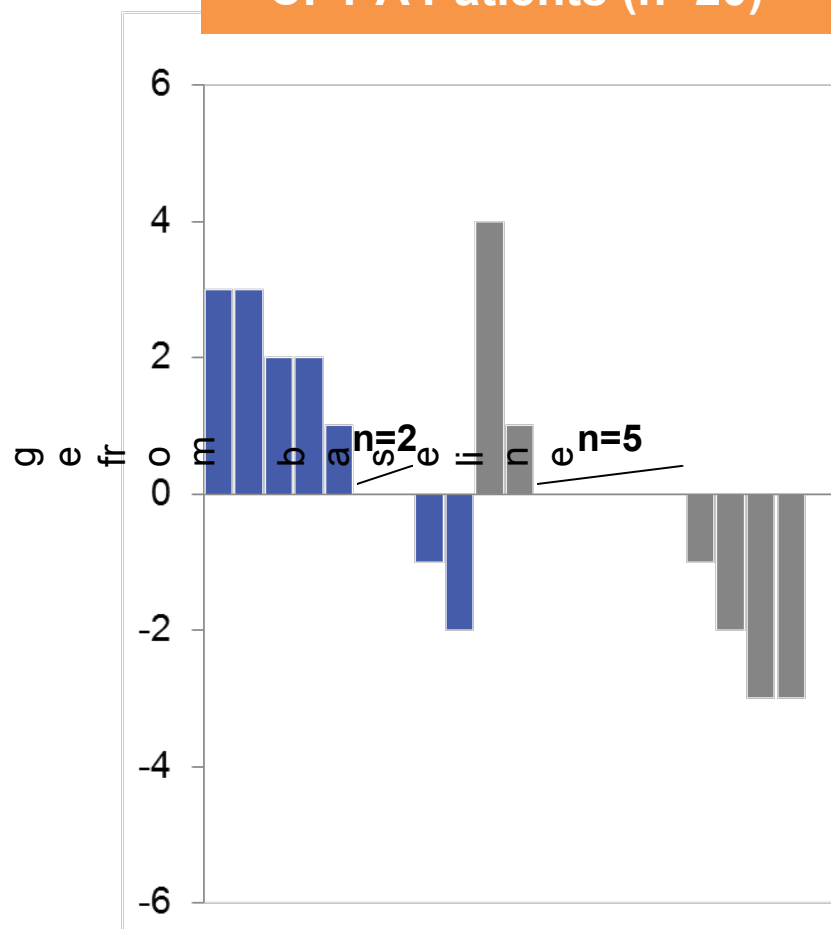
Mean Change in MELD Score from Baseline through Week 24

■ SOF + RBV

■ Observation 24 weeks

CPT A Patients (n=20)

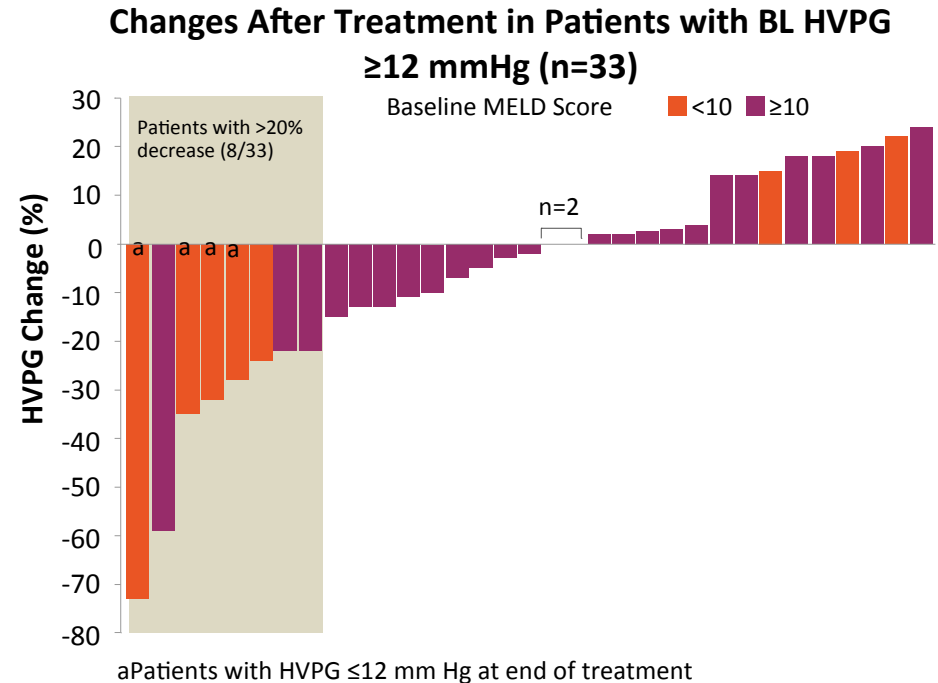
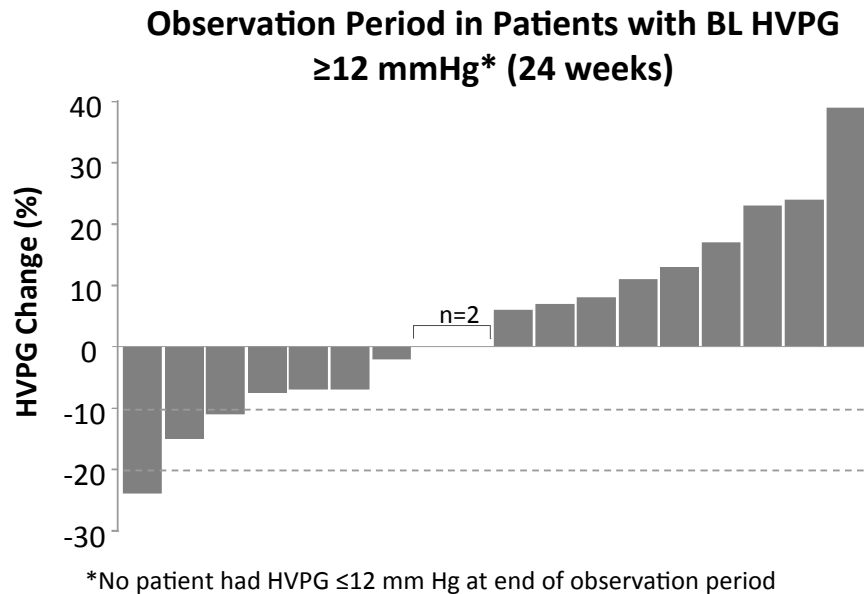
CPT B Patients (n=29*)



*1 patient had only a baseline MELD score before withdrawing consent and is not depicted.

Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension \pm decompensation

Effect of SOF+RBV on Hepatic Venous Pressure Gradient (HVPG)

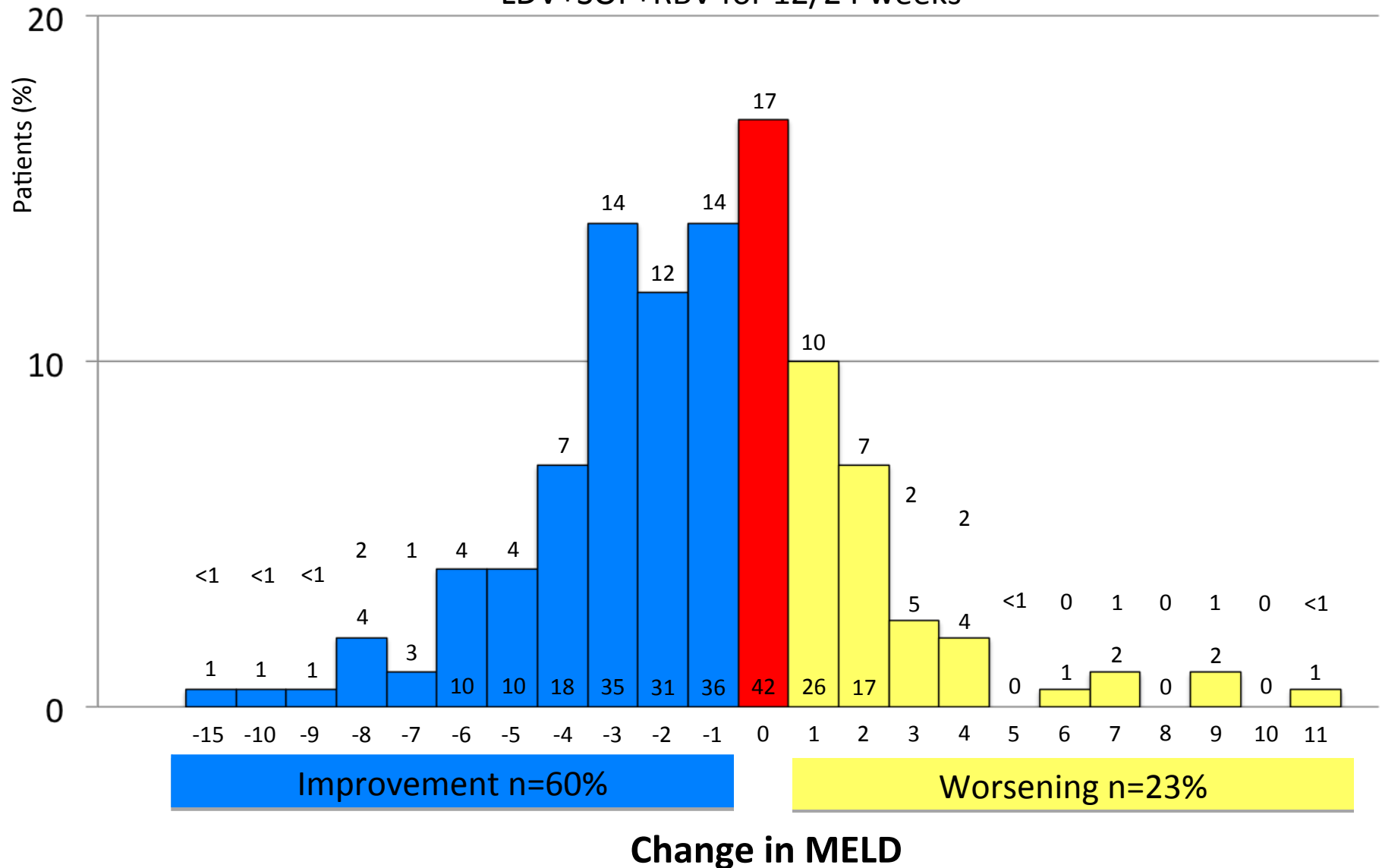


- There were clinically meaningful improvements in portal hypertension in addition to improvements in liver biochemistry, CTP and MELD scores
- The effect of SVR12 and viral suppression on HVPG is being monitored at 1 year post-treatment

A reduction in HVPG $\geq 20\%$ or below the 12-mm Hg threshold markedly reduces the risk of variceal bleeding, and varices may decrease in size

Combined Efficacy from the SOLAR-1 and SOLAR-2

LDV+SOF+RBV for 12/24 weeks



SUMMARY AND KEY CONCEPT

HCV-related cirrhosis:

a condition with a wide heterogeneity of clinical, biochemical and histological features at different risk of developing complications and with still hidden characteristics which make unpredictable the benefit of treatment irrespective to the achievement of SVR

THE NO-RETURN POINT

TAKE HOME MESSAGE 1

Clinical benefits in HCV Compensated Advanced Chronic Liver Disease (cACLD) (Well Compensated Cirrhotic Patients) Achieving a Sustained Virological Response (SVR)

Compared to NON SVR /Untreated patients does a SVR led to

| | |
|---|---------------|
| Regression of cirrhosis at histology | Yes |
| Prevention of esophageal varices development | Yes |
| Prevention of clinical decompensation | Yes |
| Reduction of hepatocellular carcinoma incidence (HCC) | Yes |
| Reduction of liver-related mortality | Yes |
| Life expectancy similar to general population | Yes |
| Reduction of all-cause mortality | Doubtful, TBD |

TAKE HOME MESSAGE 2

Clinical benefits in HCV **marginally compensated or decompensated** Cirrhotic Patients Achieving a Sustained Virological Response (SVR)

Does a SVR led to

Regression of cirrhosis

No data

Reversal of clinical decompensation

Partial, may be transient

Reduction of hepatocellular carcinoma (HCC) incidence

No data, TBD

De-listing of liver transplant

Few data

Reduction of liver-related mortality

Likely

Reduction of all-cause mortality

No data, TBD

Thank you

The opinions expressed here represent the opinion of the author. All products mentioned in the presentation should be applied according to the Product Labels.

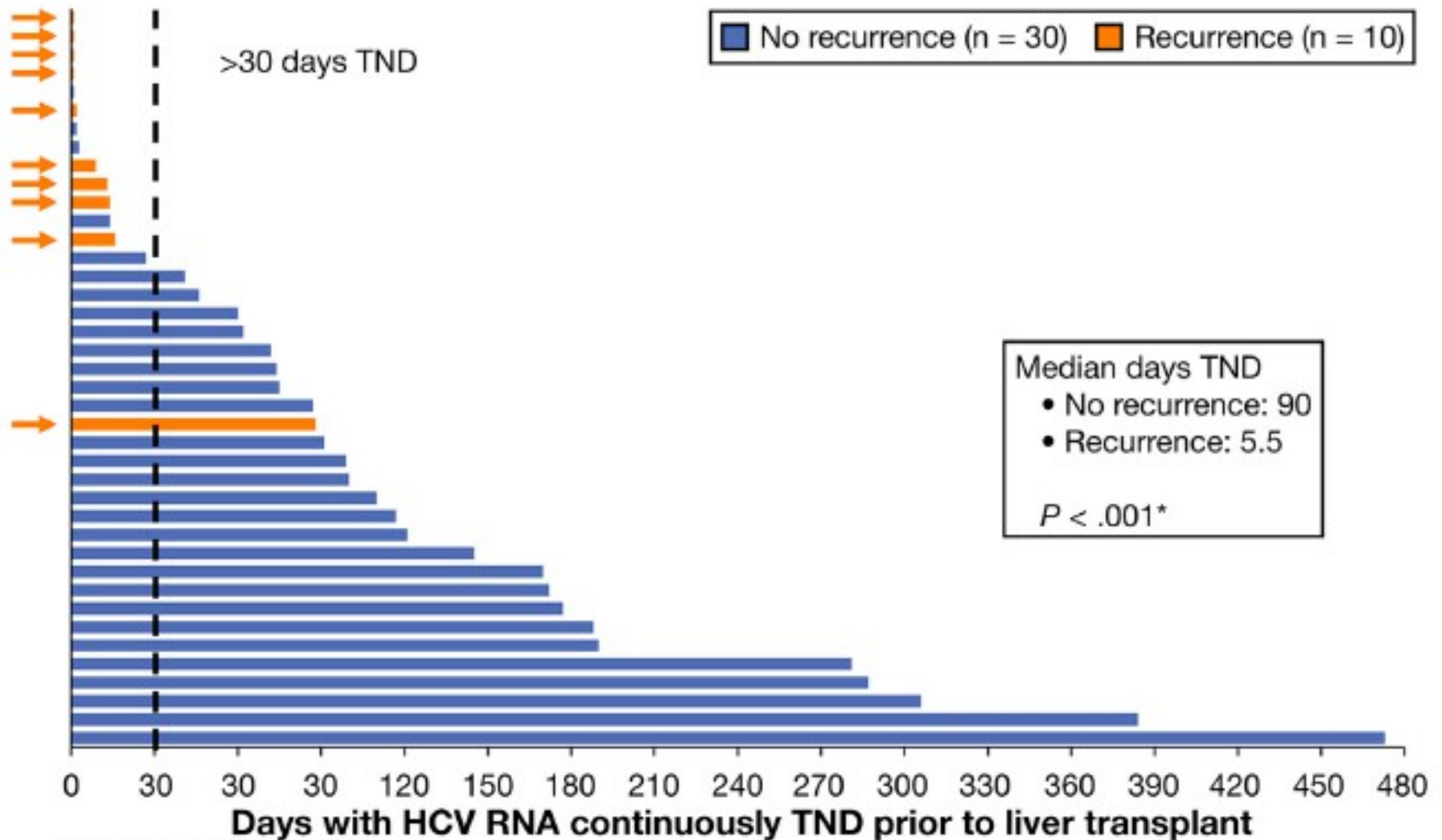
Baveno VI Consensus Statements

Criteria to Suspect cACLD

- Liver stiffness by transient elastography is sufficient to suspect cACLD in asymptomatic subjects with known causes of CLD (1b;A)
- Transient elastography often has false positive results; hence 2 measurements on different days are recommended in fasting conditions (5;D)
- **TE values <10 kPa in the absence of other known clinical signs rule-out cACLD; values between 10 and 15 kPa are suggestive of cACLD but need further test for confirmation; values >15 kPa are highly suggestive of cACLD** (1b;A)

Sofosbuvir and Ribavirin Prevent Recurrence of HCV Infection After Liver Transplantation

No recurrence/recurrence by days HCV-RNA continuously target not detected (TND) before liver transplantation



*Wilcoxon rank sum test.

The Evolutionary Stages of Hepatitis C Infection

Female sex, young age at infection

30

years

Normal
liver

Acute
infection

Chronic
infection
(50-80%)

Chronic
hepatitis

Cirrhosis
(20 %)

HCC
(1-4%/yr)

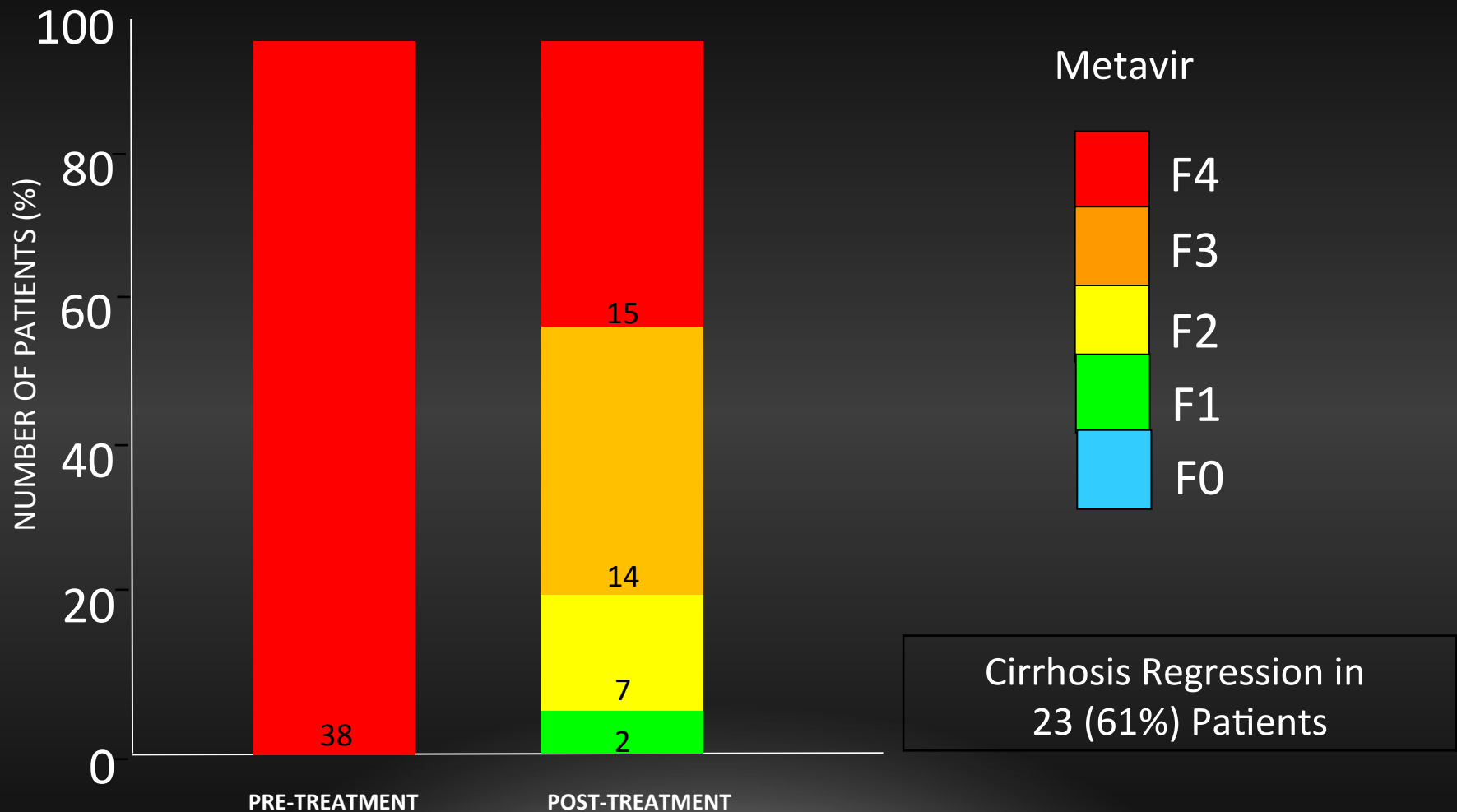
Decompensation
(3%/yr)

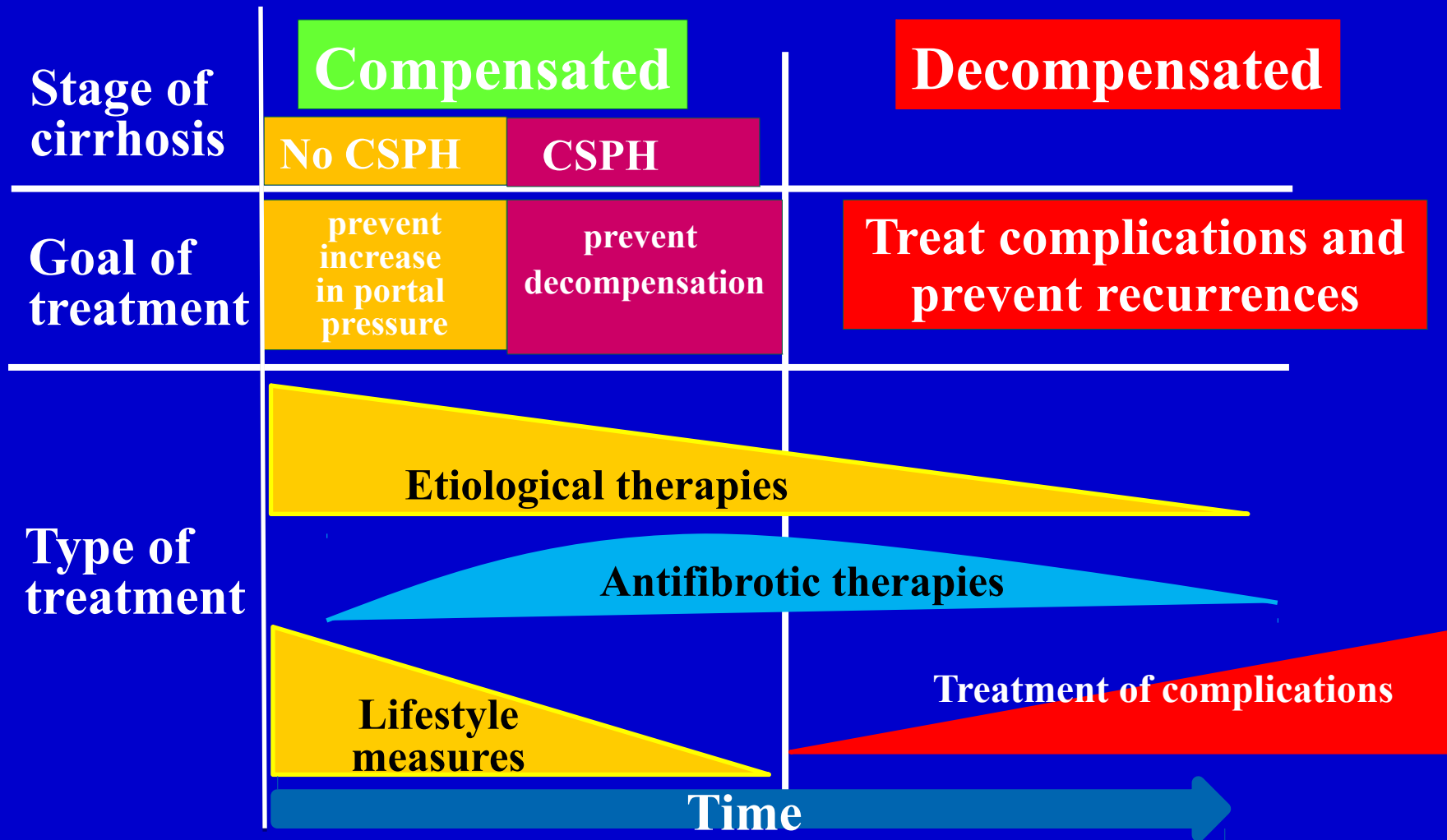
≤ 20

years

Alcohol, steatosis and/or IR,
coinfections, old age, male
sex

Rates of Cirrhosis Regression According to the METAVIR Scoring System





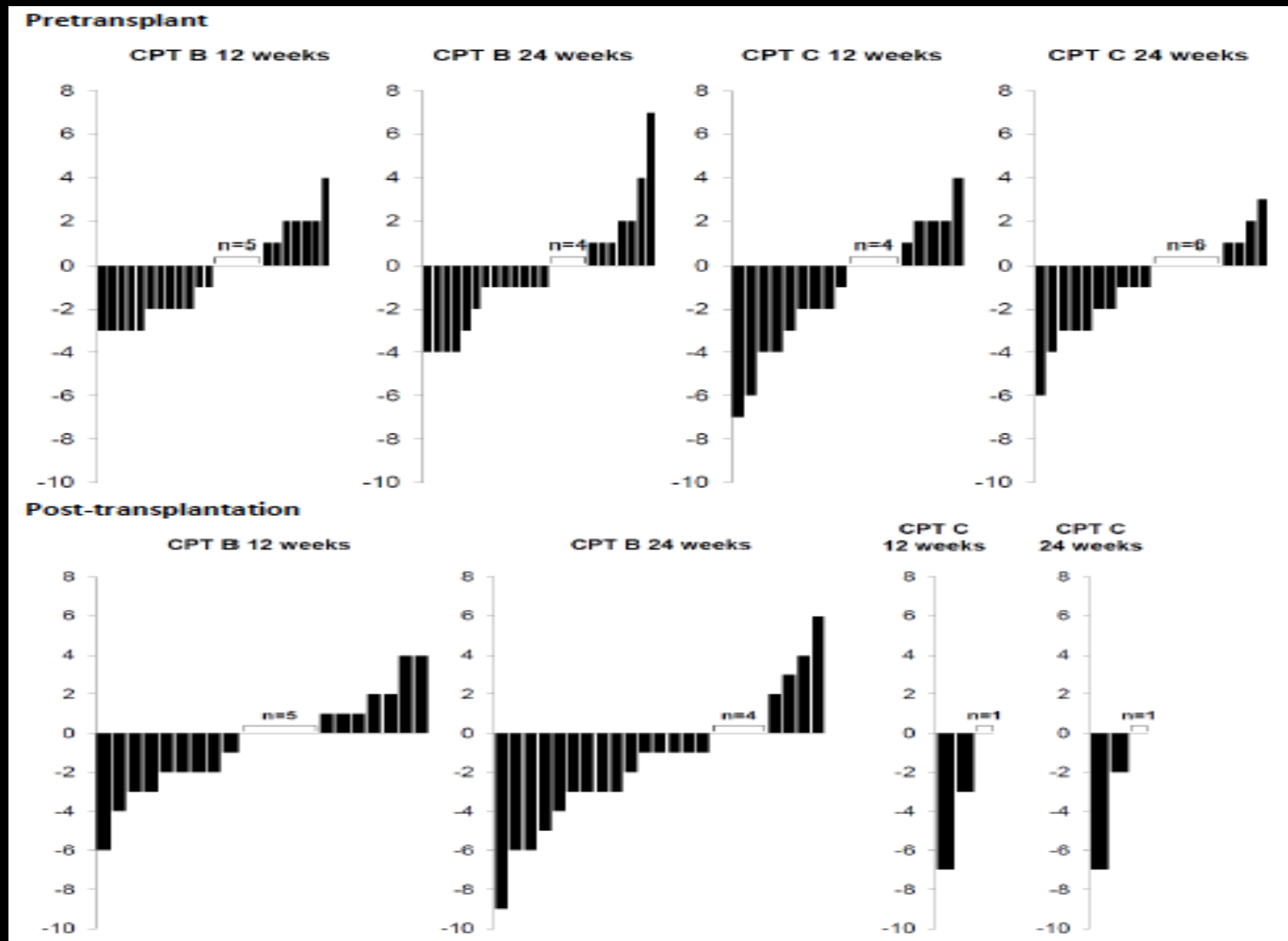
Infections occurring during Peg IFN+RBV treatment

| Ref. | Pts n. | Type of Pts | Infections | Factors associated |
|-----------------------|-----------|----------------------------|---|--|
| 1 | 255 | F3-F4 Metavir 17% | 12% (24 / 100 pts / yr) | Neutropenia only in respiratory infection |
| 2 | 319 | F3-F4 Metavir 34% | 23% (41/100 pts / yr) | Age> 60 (not neutropenia) |
| 3 | 119 | Cirrhosis 15% | 18% | None with neutropenia |
| 4 | 30 | OLT listed (50% CTP A) | 13% | n.a. |
| 5 case- control | 66 | Decompensated cirrhosis | 28% { 0.45 / 1000pts / mo. OR = 2.95 (0.93-9.3) } | CTP C; neutrophils < 900 |

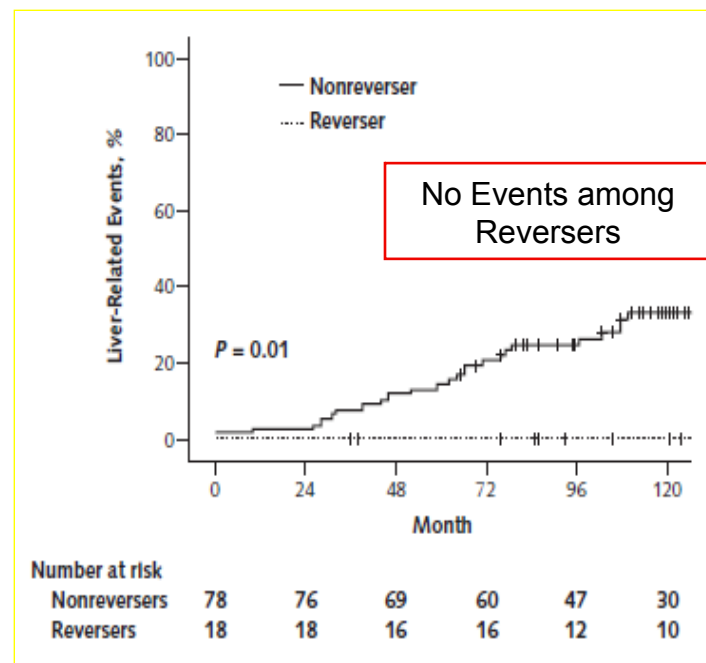
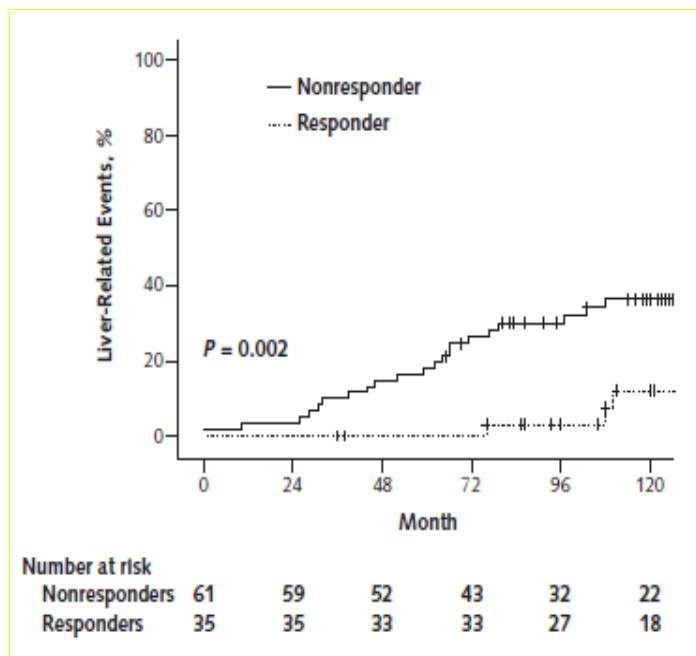
1. Puoti et al., *Antiviral Ther.* 2008; 2 Antonini et al., *Infection* 2008; 3. Soza et al. *Hepatology*. 2002; 4 Forns et al., *J. Hepatology*. 2003; 5. Iacobellis et al. *J. Hepatology* 2007

SOLAR-1: LDV+SOF+RBV in G1/G4 HCV patients with decompensated cirrhosis

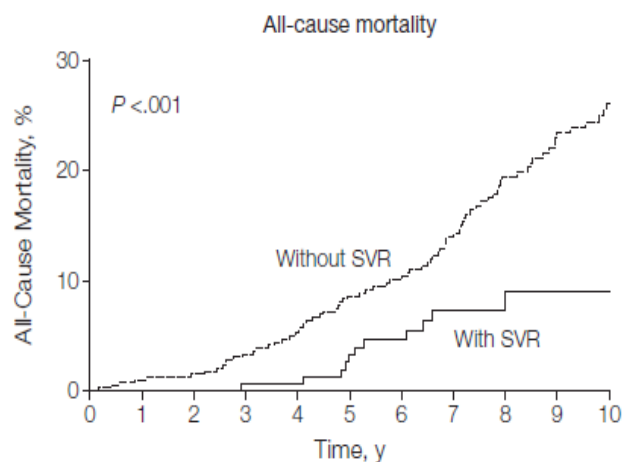
Change in MELD Score from Baseline to Follow-up Week 4 in CPT B and C Patients



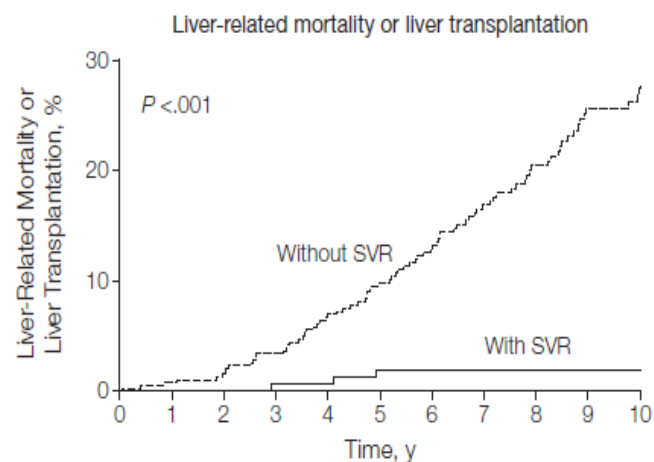
The Impact of Cirrhosis Regression on Clinical Events



Survival Outcomes in Patients with Advanced Hepatic Fibrosis Due to HCV



| | | | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| No. at risk | | | | | | | | | | | |
| Without SVR | 405 | 393 | 382 | 363 | 344 | 317 | 295 | 250 | 207 | 164 | 135 |
| With SVR | 192 | 181 | 168 | 162 | 155 | 144 | 125 | 88 | 56 | 40 | 28 |



| | | | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| No. at risk | | | | | | | | | | | |
| Without SVR | 405 | 392 | 380 | 358 | 334 | 305 | 277 | 229 | 187 | 146 | 119 |
| With SVR | 192 | 181 | 168 | 162 | 155 | 144 | 125 | 88 | 56 | 40 | 28 |

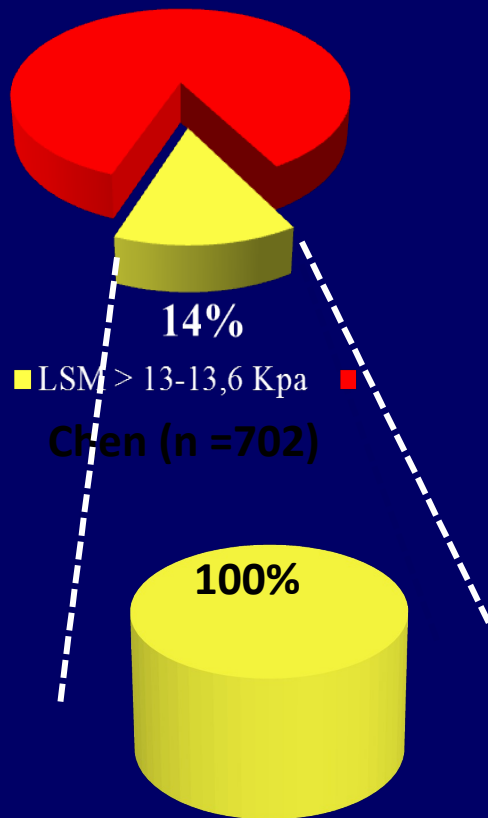
Baveno VI Consensus Statements

Stage of cirrhosis and goal of treatment

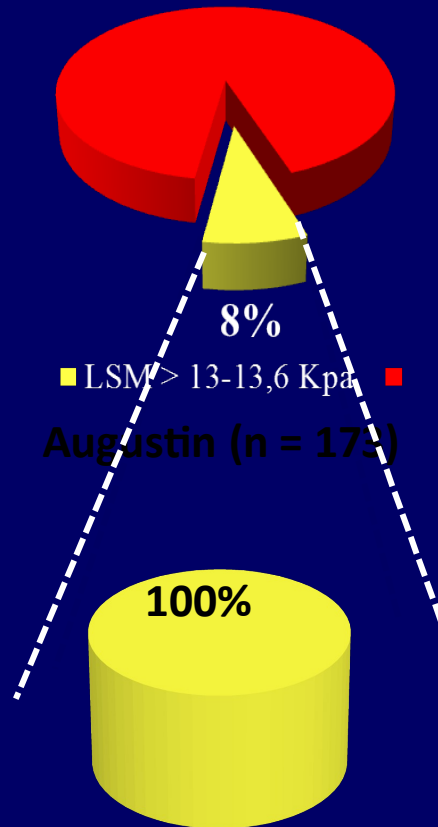
- Management of patients with cirrhosis should focus on preventing the advent of all complications whilst in the compensated phase (**1b;A**).
- Due to different prognosis, **patients with compensated cirrhosis should be divided in those with and without clinically significant portal hypertension (CSPH) (1b;A). The goal of treatment in the first is to prevent CSPH while in the second is to prevent decompensation.**

Chronic liver disease with no signs of liver cirrhosis

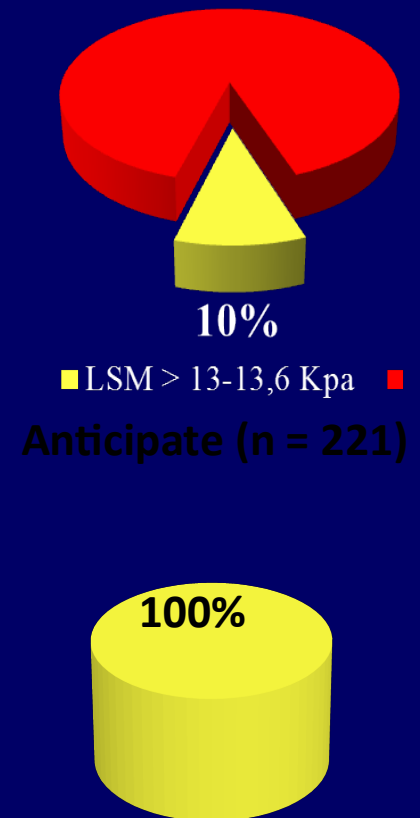
Chen (n = 702)



Augustin (n = 173)



Kim (n = 2876)



PATIENTS WITH OCCULT ADVANCED Chronic liver disease

Modified from Augustin S et al. Baveno VI Proceedings,

Compensated Advanced Chronic Liver Disease

For these patients, the alternative term “**compensated advanced chronic liver disease (cACLD)**” has been proposed to better reflect that the spectrum of severe fibrosis and cirrhosis is a continuum in asymptomatic patients, and that distinguishing between the two is often not possible on clinical grounds.

These patients deserve:

- Closer follow-up
- HCC screening
- Consider evaluation for varices and CSPH

Outcome of 352 patients with compensated cirrhosis due to HCV infection

| Antiviral therapy | Patients | Hepatic decompensation | Hepatocellular carcinoma | Hepatic Mortality [†] |
|----------------------------------|-----------|------------------------|--------------------------|--------------------------------|
| | N (%) | N (% per year) | N (% per year) | N (% per year) |
| Untreated | 159 (45%) | 62 (3.3%) | 54 (2.8) | 61 (2.9) |
| Non-SVR | 165 (47%) | 70 (3.6%) | 57 (2.9) | 72 (3.3) |
| SVR | 28 (8%) | 2 (0.4) | 7 (1.7) | 5 (1.1) |
| P-value (Untreated vs. non SVR) | | 0.58 | 0.83 | 0.46 |
| P-value (Non SVR vs. SVR) | | 0.0005 | 0.17 | 0.01 |

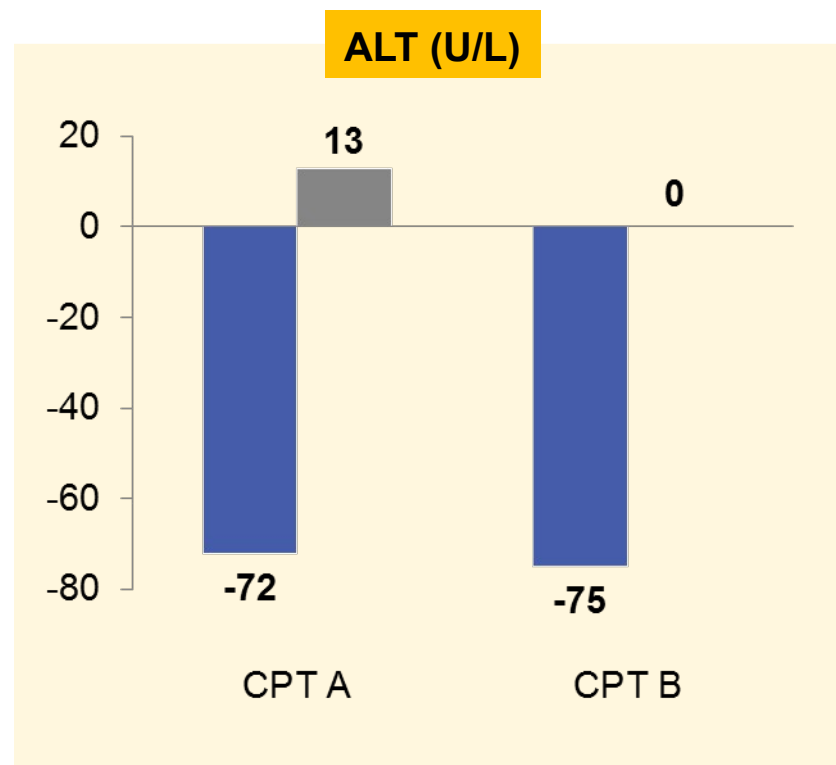
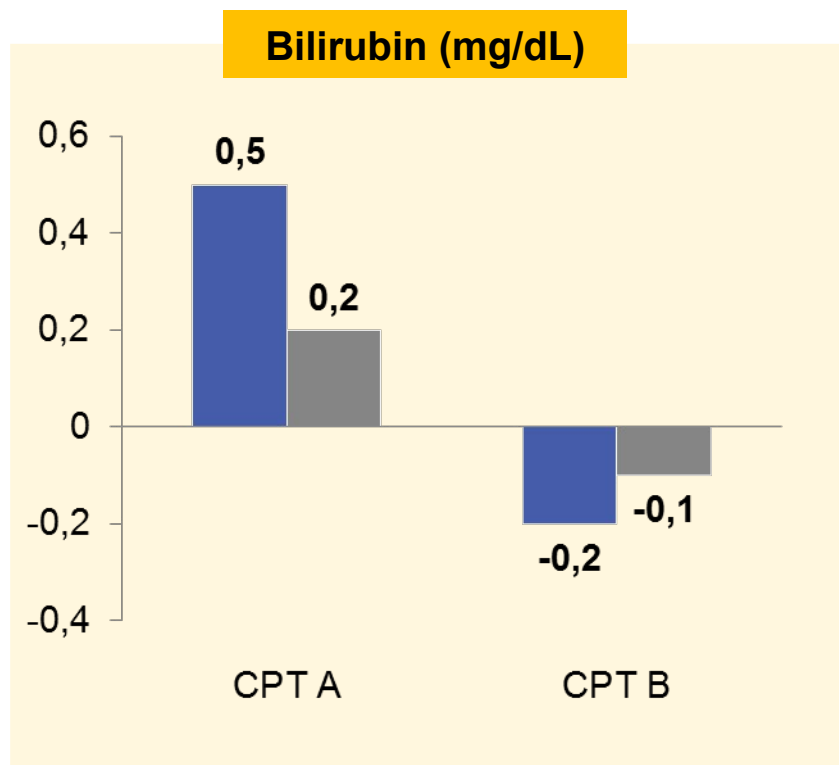
SVR: Sustained Virological Response; † includes Orthotopic Liver Transplantation (OLT).

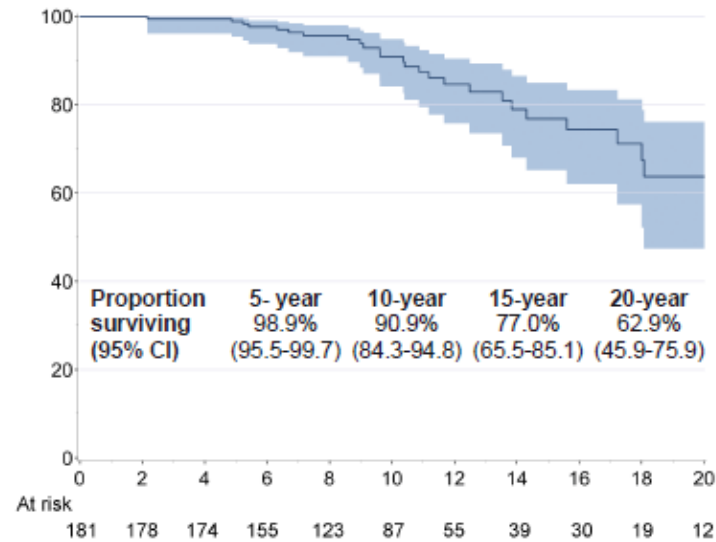
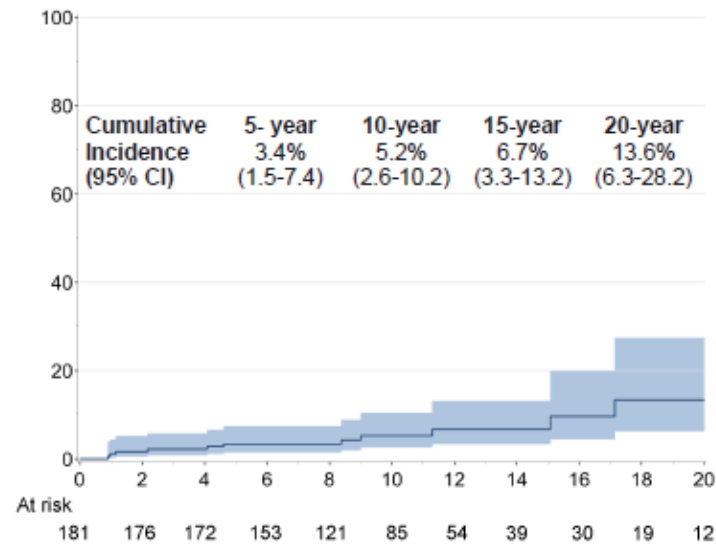
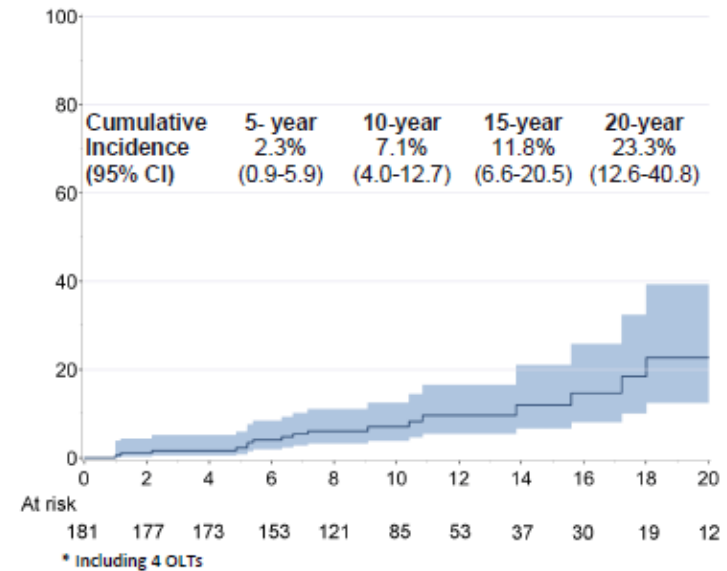
Updated from Bruno S, et al. Am J Gastroenterol 2009

Sofosbuvir and Ribavirin in patients with cirrhosis and portal hypertension \pm decompensation

Laboratory Results: Mean Changes from Baseline to Week 24

■ SOF+RBV ■ Observation 24 weeks



A Overall survival**B Hepatic decompensation****C Liver related mortality*****D Hepatocellular carcinoma**