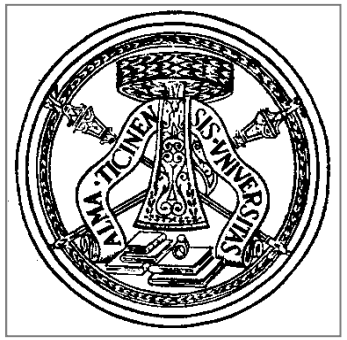

Managing Cirrhotic Patients With Hepatitis C

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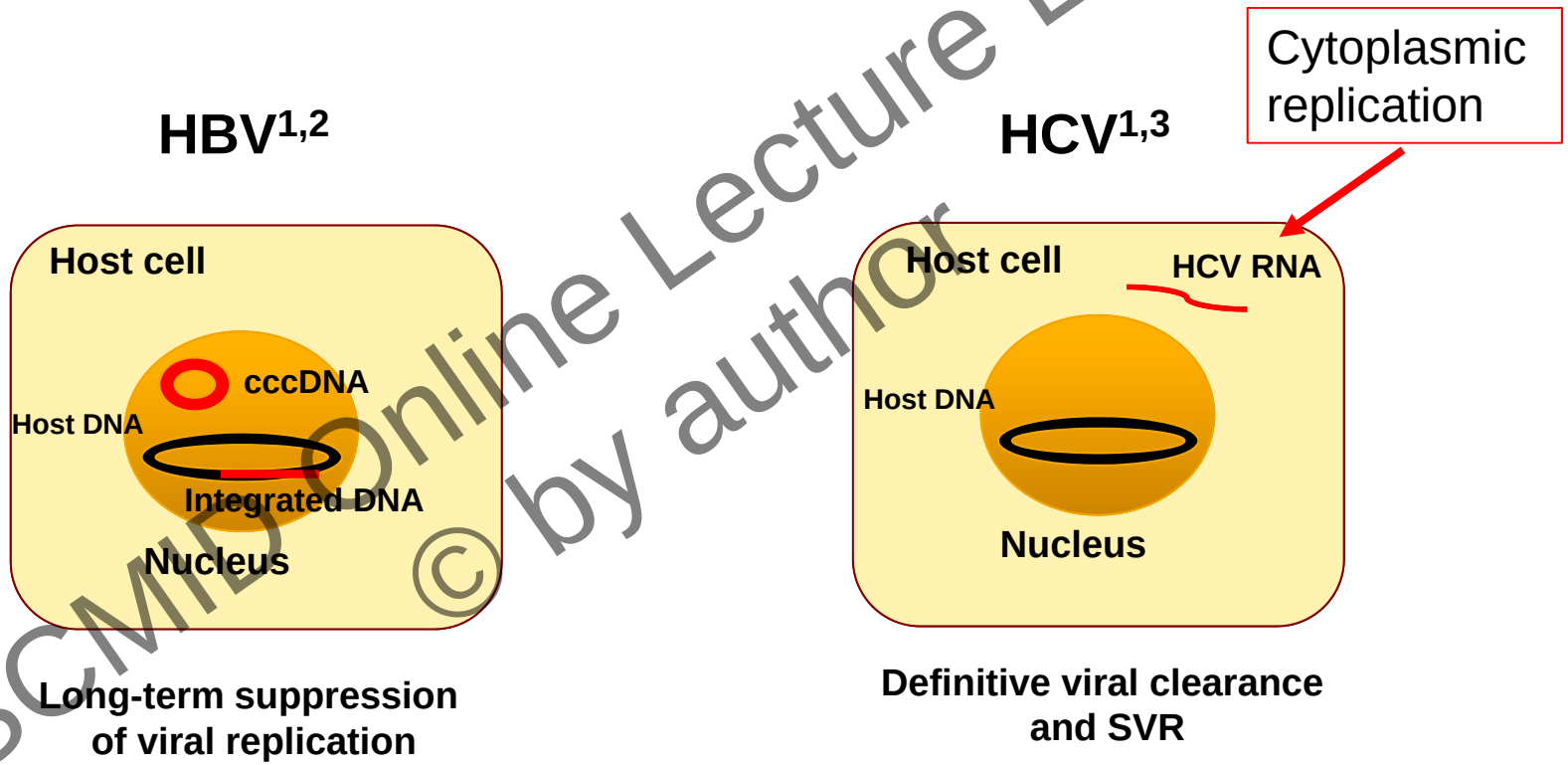
We Have Declared Victory Over HCV But…
We Are Not Quite There Yet

HCV Infection Is Curable



Adapted from 1. Soriano V, et al. J *Antimicrob Chemother* 2008;62:1-4. 2. Locarnini S and Zoulim F. *Antiviral Therapy* 2010;15 (suppl 3):3-14. 3. Sarrazin C and Zeuzem S. *Gastroenterology* 2010;138:447-462.

Indications for Treatment of Chronic Hepatitis C in 2016: EASL Clinical Practice Guidelines

- **Treatment should be prioritized in:**
  - Patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in patients with clinically significant extra-hepatic manifestations (A1).
  - Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18-20 should be transplanted first and treated after transplantation (B1).

Current Treatment Options of Compensated Cirrhosis

- Sofosbuvir + Simeprevir: G4
- Sofosbuvir + Daclatasvir: G1-6
- Sofosbuvir/Ledipasvir FDC: G1, 4, 5, 6
- Paritaprevir/r + Ombitasvir FDC: G4,
  + Dasabuvir: G1
- Grazoprevir + Elbasvir FDC: G1-4
- Sofosbuvir + Velpatasvir FDC: Pangenotypic
- Ribavirin added to combos in IFN-experienced patients
- Treatment duration: 12 (usually + RBV) - 24 weeks

First Line DAA Regimens for Patients With Decompensated Cirrhosis According to Current Guidelines[1-6]

HCV Genotype	Therapy
GT1	- Sofosbuvir/Velpatasvir + RBV° for 12 weeks* - Sofosbuvir/Ledipasvir + RBV° for 12 weeks*
GT2	- Sofosbuvir/Daclatasvir + RBV° for 12 weeks* - Sofosbuvir/Velpatasvir + RBV° for 12 weeks*
GT3	- *Sofosbuvir/Daclatasvir + RBV° for 12 weeks* - Sofosbuvir/Velpatasvir + RBV° for 12 weeks*
GT4	- Sofosbuvir/Velpatasvir + RBV° for 12 weeks* - Sofosbuvir/ Ledipasvir + RBV° for 12 weeks*
GT5-6	- Sofosbuvir/Daclatasvir + RBV° for 12 weeks* - Sofosbuvir/Velpatasvir + RBV° for 12 weeks*#

Use of PI not recommended in CTP class B-C and pts with history of prior decompensation

- °low initial dose of RBV (600 mg) is recommended, increased as tolerated
- *RBV intolerance: prolongation up to 24 weeks should be evaluated
- # no data on decompensated cirrhosis exits, based on data from studies with compensated cirrhosis

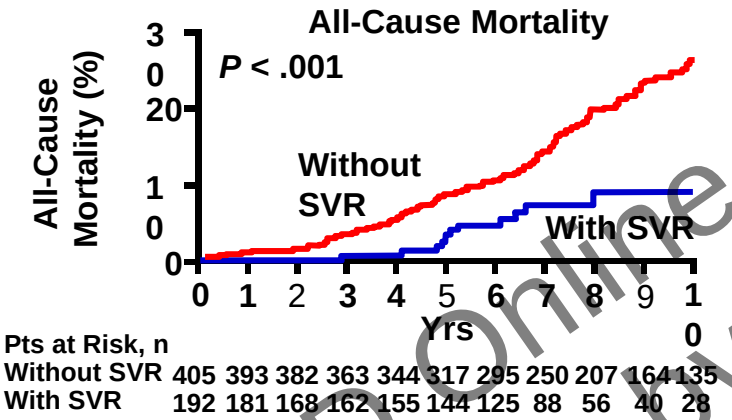
1. Saxena V, et al. Hepatology 2015; 62: 715-25. 2. Jacobson I, et alJ Hepatol 2015 (EASL abstract O008). 3. Charlton M, et al. Gastroenterology 2015; 149: 649-59. 4. Foster GR, et al. J Hepatol 2016; 64: 1224-31. 5. European Association for the Study of the Liver (EASL). Recommendations on Treatment of Hepatitis C 2016. J Hepatol 2016; epub ahead of print. 6. Mücke MM, et al. Liver Int 2017, in press.

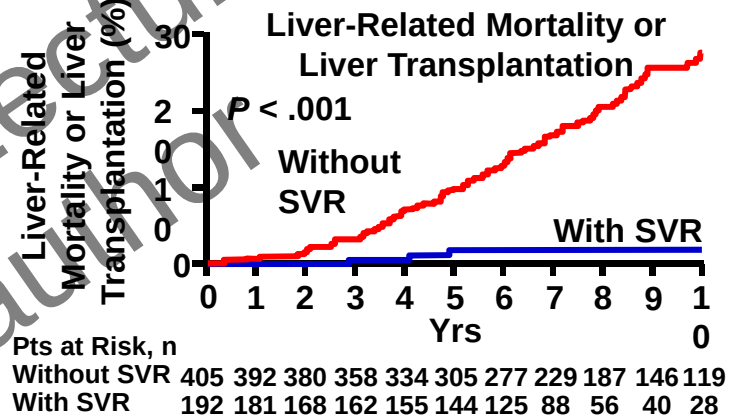
Clinical Benefits in Compensated Cirrhosis Achieving SVR

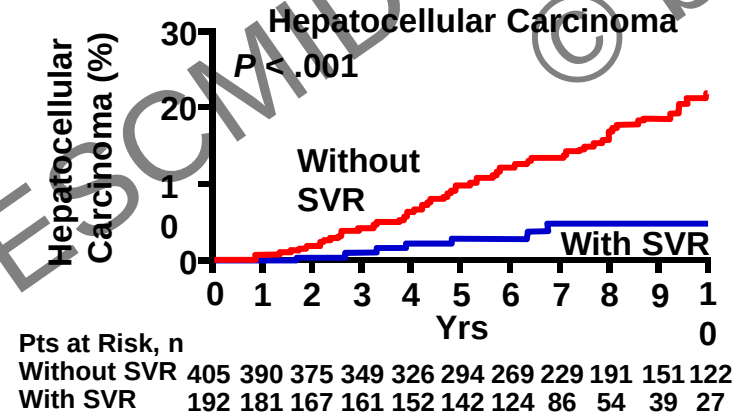
Compared to NON SVR /Untreated patients does an SVR lead to:

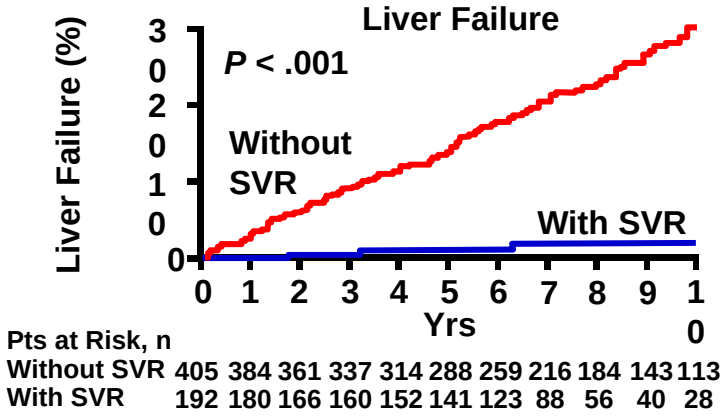
- **Regression of cirrhosis at histology** — **Yes**
- **Prevention of esophageal varices** — **Yes**
- **Prevention of clinical decompensation** — **Yes**
- **Reduction of HCC** — **Yes**
- **Reduction of liver-related mortality** — **Yes**
- **Life expectancy similar to general population** — **Yes**
- **Reduction of all-cause mortality (except extrahepatic tumors)** — **Yes**

Survival Outcomes in Pts With CHC and Advanced Fibrosis With or Without SVR to PEG-IFNα + RBV







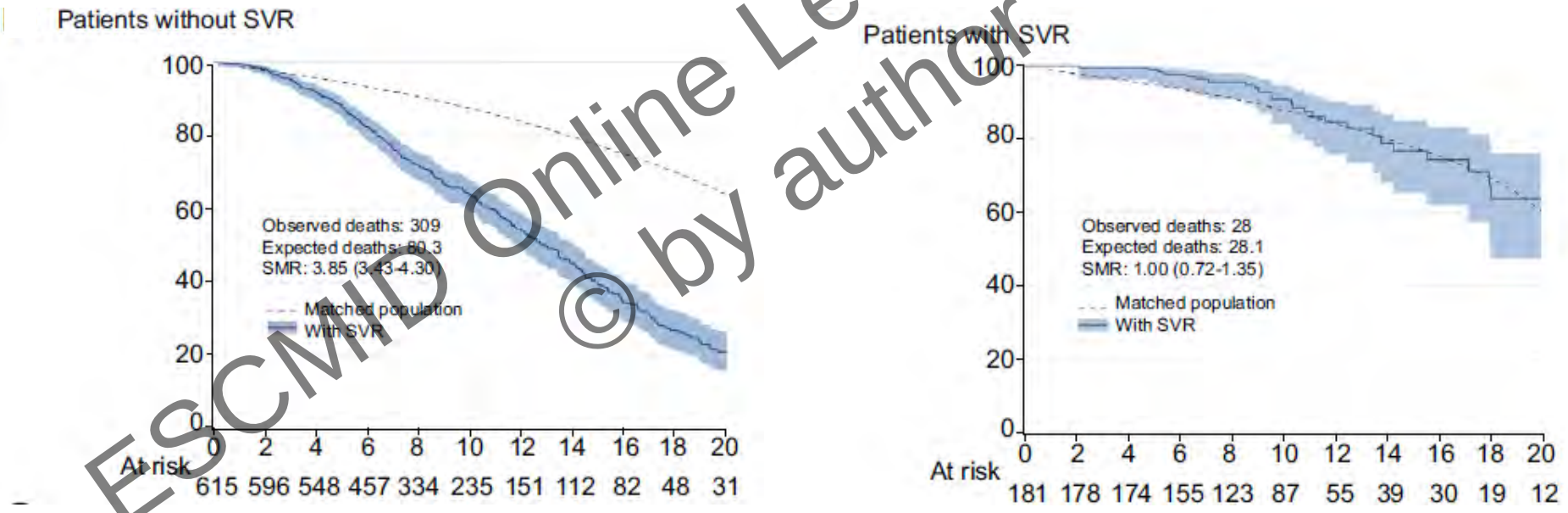


Van der Meer AJ, et al. *JAMA* 2012;308:2584-2593.

Survival of HCV-Infected Cirrhotic Patients Who Achieved SVR Is Comparable to the General Population

Predictors of Death:

- **Male sex**
- **Platelets <80K**

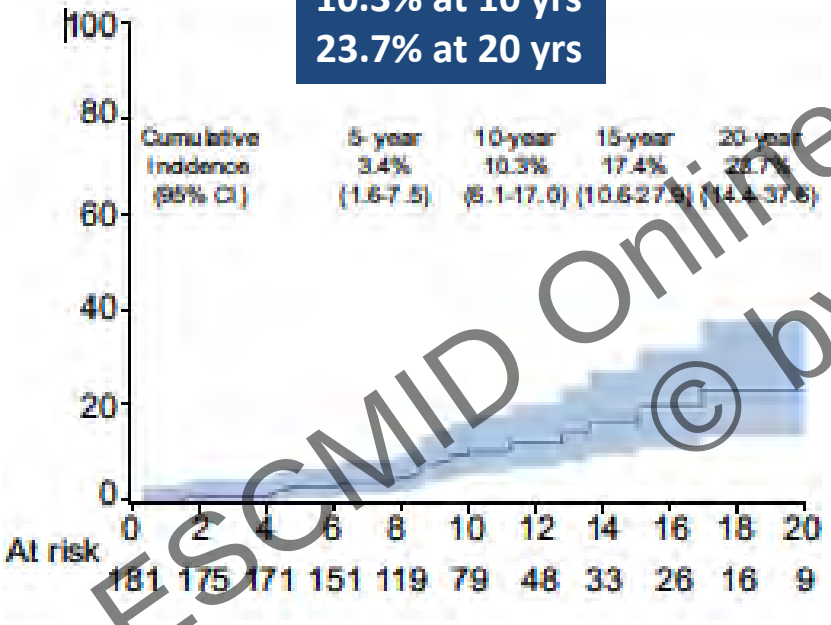


Bruno S et al. *J Hepatol* 2016 Jun;64:1217-23

Liver-Related Complications in Patients with Compensated Cirrhosis & SVR

Hepatocellular Carcinoma

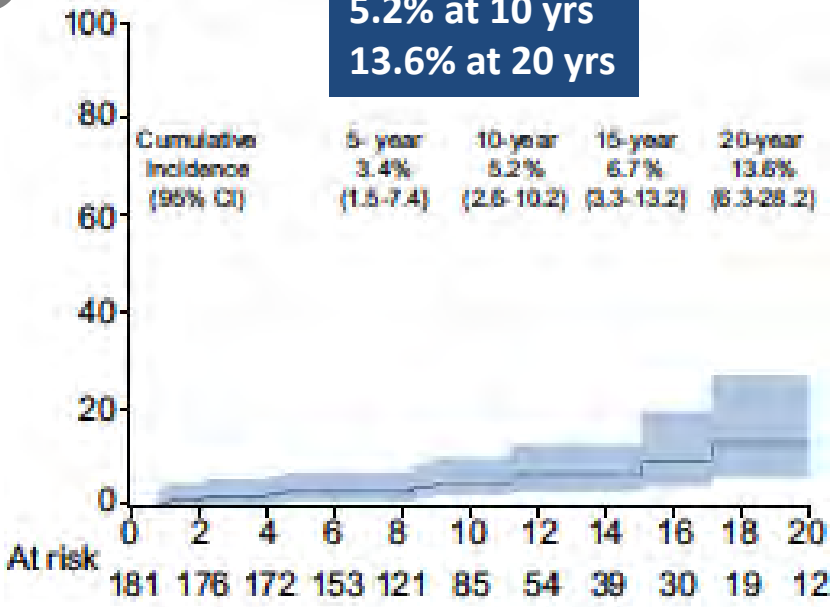
10.3% at 10 yrs
23.7% at 20 yrs



CP-A Cirrhosis
IFN-based therapy
No alcohol info

Liver Decompensation

5.2% at 10 yrs
13.6% at 20 yrs



Bruno S et al. *J Hepatol* 2016 Jun;64:1217-23

Factors Associated with Decompensation in Patients with Advanced Fibrosis Achieving SVR

Most consistent	Emerging?
Male sex	Diabetes
Low albumin	Age ≥ 65 y.o.
Low platelet count	

Factors Associated with HCC in Patients with Advanced Fibrosis Achieving SVR

Most Frequently Cited	Emerging?
Older age	Diabetes
Male sex	LSM post-SVR >12 kPa
Low albumin levels	Elevated AFP post-SVR (>10)
Alcohol use/abuse	Genotype 3

Bruno S, J Hepatol 2016; El-Serag, Hepatology, 2016; Hedenstierna M, CID 2016; Nagaoki Y, J GH, 2016; Wang JH Liver International 2016

HCC Risk Remains High after SVR with Peg-IFNα ± RBV

- Retrospective VA cohort study, 22,028 HCV pts treated with PegIFN ± RBV from 1999-2009
- HCC incidence (x 1000 PY): 3.27 SVR vs 13.2 non SVR (HR: 0.358)

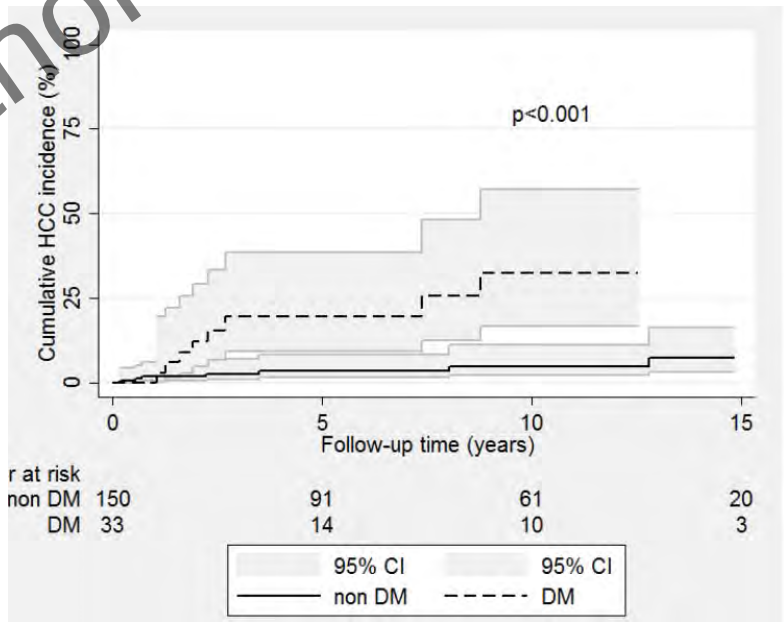
Predictor of HCC Following SVR*	HR (95% CI)	*P* Value
Cirrhosis at SVR	4.45 (2.53-7.82)	< .0001
Age at SVR, yrs (vs < 55 yrs)		
▪ 55-64	2.40 (1.53-3.77)	.0002
▪ 65 or older	4.69 (2.04-10.78)	.0003
Diabetes	2.07 (1.35-3.20)	.0010
HCV GT (vs GT1)		
▪ HCV-2	0.56 (0.32-1.01)	.0522
▪ HCV-3	1.91 (1.14-3.18)	.0131

*Cox proportional hazards model adjusted for competing risk of death.

Risk of HCC After SVR

- **Swedish cohort study of F3/F4 with SVR followed for 7.8 yrs**
- **N=17* developed HCC: incidence in those with F4 was 1/100 p-yrs**
- **Risk decreased significantly 2 years after achieving SVR**

Multivariate	Original[c]			Adjusted[d]		
	HR	95% CI	p=	HR	95% CI	p=
Male sex	3.36	0.69-16.3	0.13	5.22	0.60-45.4	0.14
Age at SVR, (per year)	1.07	0.99-1.16	0.11	1.06	0.97-1.17	0.20
DM	3.23	1.09-9.60	0.035	6.26	1.70-23.1	0.006
Albumin levels < 35 g/dl	4.40	1.32-14.7	0.016	6.23	1.55-25.0	0.01



* All had F4 except for 1 patient (based on biopsy or elastography)

Hedenstierna M, CID 2016

Musts and Unmet Needs in Pts Achieving SVR

- Counselling on the need of continuous HCC surveillance in cirrhotic patients
  - Patients with F3 stage + risk factors do warrant HCC surveillance
- Risk modification to reduce HCC risk?
  - Diabetes, alcohol
- Can HCC surveillance stop at some stage?
- Establish the risk reduction in HCC achievable with DAA-associated SVR

Defining the Point of No Return

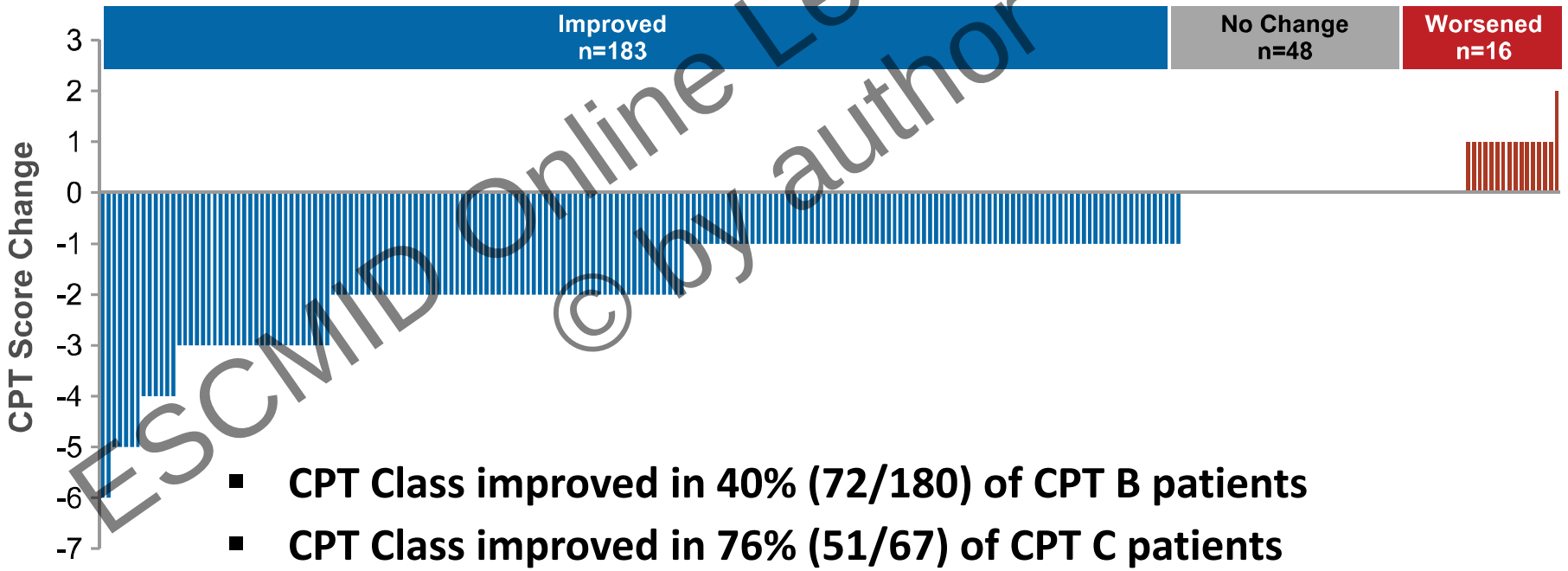
Clinical Benefits in HCV Decompensated Cirrhosis Achieving SVR

Does an SVR lead to:

▪ Regression of cirrhosis	No data
▪ Reversal of clinical decompensation	Definitive/partial/transient
▪ Reduction of HCC	No data
▪ Delisting from liver transplant	Possible
▪ Reduction of liver-related mortality	Likely
▪ Reduction of all-cause mortality	No data

CPT Score Change from Baseline to FU-24 in CPT B/C Patients Who Achieved SVR12 After DAA Therapy

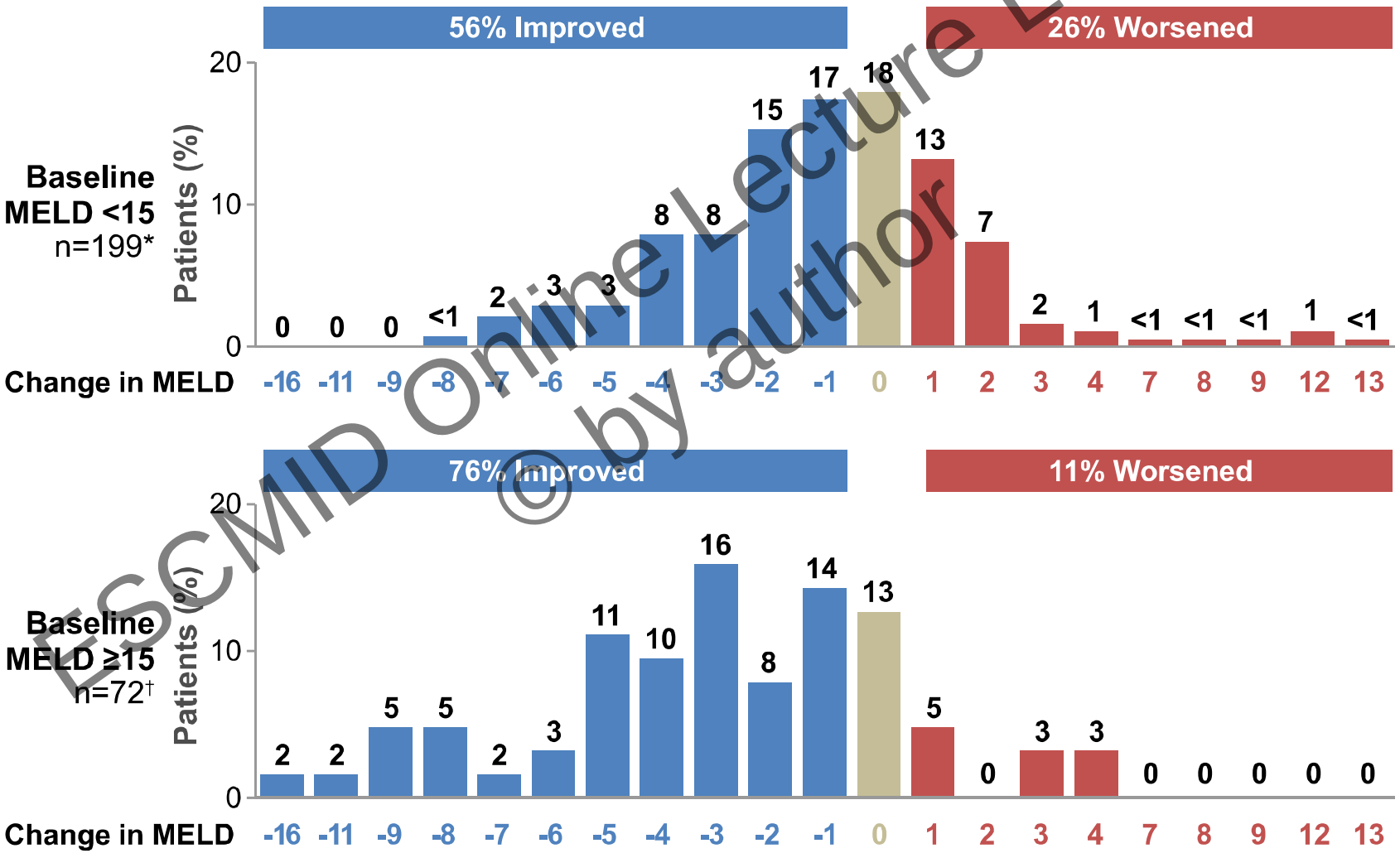
- 247 patients with decompensated cirrhosis who achieved SVR12
- CPT score change from baseline to 24 Weeks post-SVR in CPT B/C patients



- CPT Class improved in 40% (72/180) of CPT B patients
- CPT Class improved in 76% (51/67) of CPT C patients
  - 64% (43/67) improved to CPT B; 12% (8/67) improved to CPT A

Gane E, APASL 2016

MELD Score Change From Baseline to 24 Weeks Post-Treatment in CPT B/C Patients

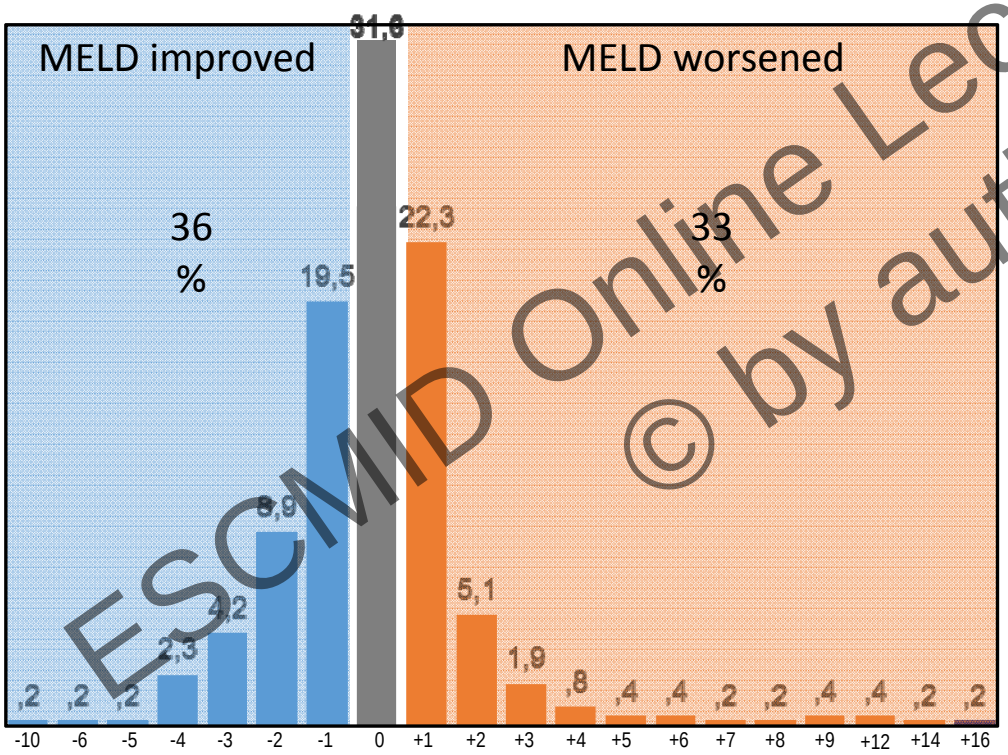


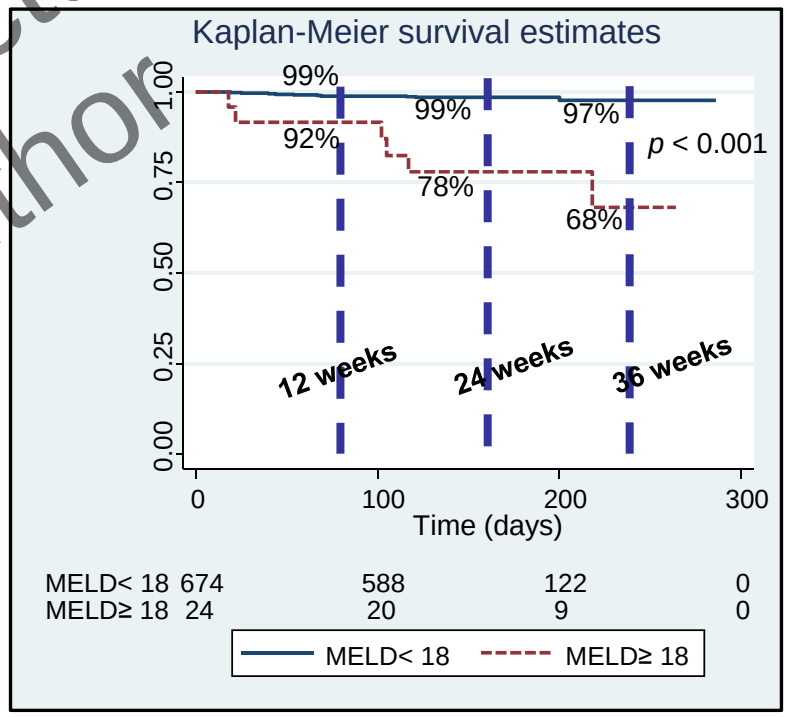
No FU-24 assessment for *9 patients, †9 patients.

Gane E, APASL 2016

Treatment of HCV Infection in Patients With Advanced Cirrhosis. The Hepa-C Registry

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





Fernàndez-Carrillo, et al. ILC2016 Barcelona

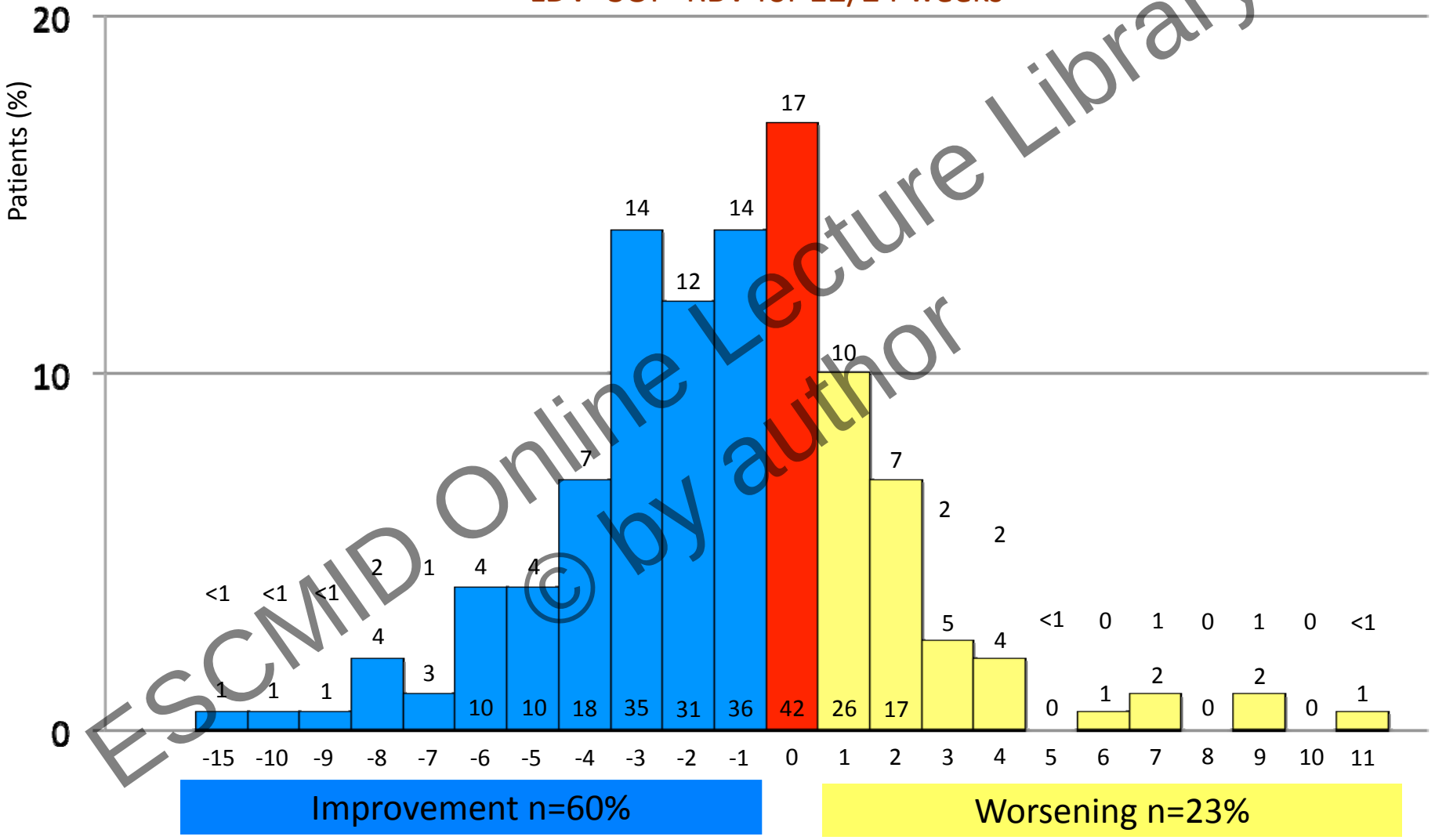
Changes in Measurements of Hepatic Decompensation After DAA Therapy in Pts With Chronic HCV Infection and Advanced Liver Disease

	Solar-1 [78]	Solar-2 [78]	Ally-1 [76]	Astral-4 [79]
Number of patients evaluated	93	81	39	250
Time at evaluation	SVR-4	SVR-24	SVR-12	SVR-12
MELD changes				
Improvement	67%	73%	40%	54%
In CTP-B cirrhosis	64%	65%	43%	54%
In CTP-C cirrhosis	70%	83%	67%	-
Worsening	17%	16%	40%	25%
In CTP-B cirrhosis	17%	20%	43%	25%
In CTP-C cirrhosis	18%	11%	0%	-
CTP changes				
Improvement	67%	77%	76%	47%
Worsening	8%	8%	12%	11%

van der Meer AJ, Berenguer M. *J Hepatol* 2016;65:S95-S108.

Combined Efficacy from the SOLAR-1 and SOLAR-2

LDV+SOF+RBV for 12/24 weeks



Change in MELD

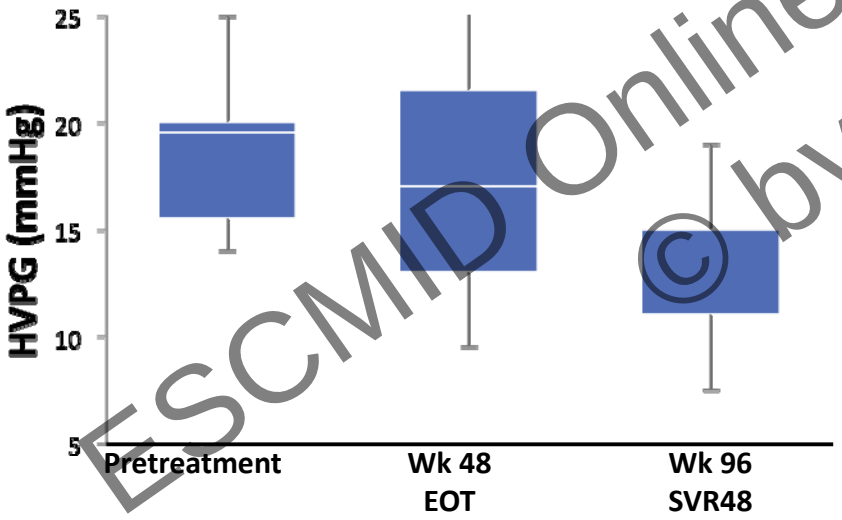
250 patients had no assessment at follow-up week 12

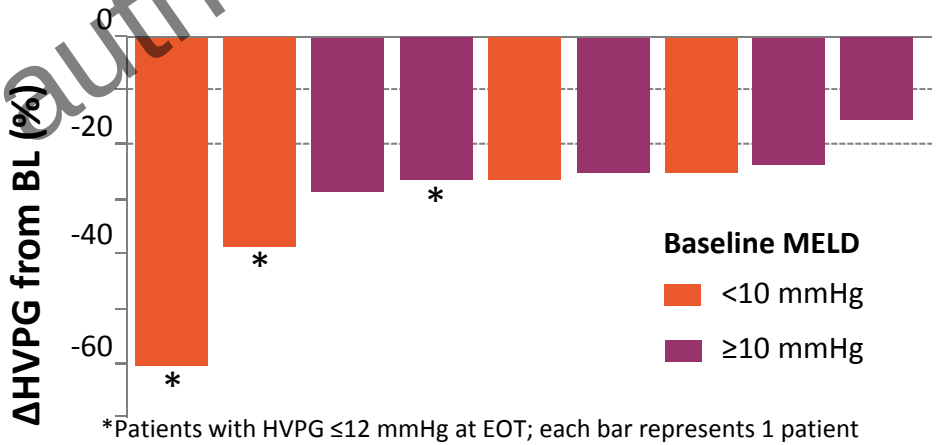
Gane E, et al, AASLD 2015

Does DAA Therapy Reduce Portal Hypertension?

- 46 had paired HVPG at baseline and end-of-treatment
- 9 had follow-up HVPG at 48 weeks post-treatment

HVPG % change at PTW48 in patients with BL HVPG ≥12 mmHg who achieved SVR12 (n=9)





*Patients with HVPG ≤12 mmHg at EOT; each bar represents 1 patient

- Mean 29% decrease in HVPG
- HVPG <12 mmHg in 1/3 pts

- 8/9 had >20% ↓HVPG

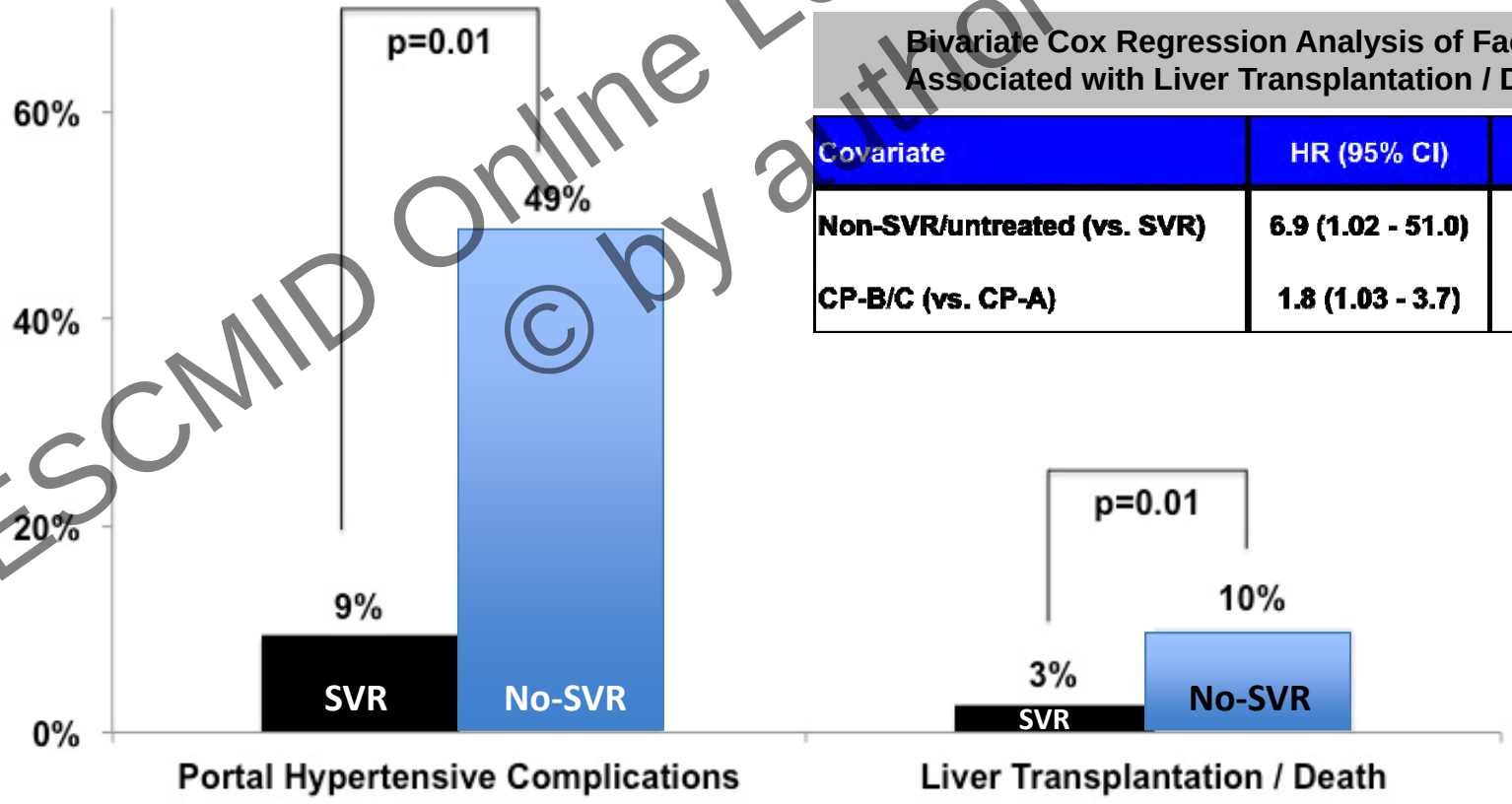
*Patients with HVPG ≤12 mmHg at EOT; each bar represents 1 patient

SOF+RBV for 48 weeks in CTP-A/B + HVPG >6mmHg

Afdhal, et al. EASL 2016; Poster #LBP518

SVR Associated with Fewer Cirrhosis-Related Complications

- Multicenter study of patients with compensated/decompensated cirrhosis treated with SMV/SOF ±RBV for 12-24 wks; 84% achieved SVR
- Compared to 269 untreated/non-SVR matched controls
- Median MELD=9 and CP score 6



Bivariate Cox Regression Analysis of Factors Associated with Liver Transplantation / Death

Covariate	HR (95% CI)	p-value
Non-SVR/untreated (vs. SVR)	6.9 (1.02 - 51.0)	0.03
CP-B/C (vs. CP-A)	1.8 (1.03 - 3.7)	0.04

Saxena et al. AASLD 2015, Abstract #1825..

Can We Identify Patients Who Are Unlikely to Benefit from DAA Therapy?

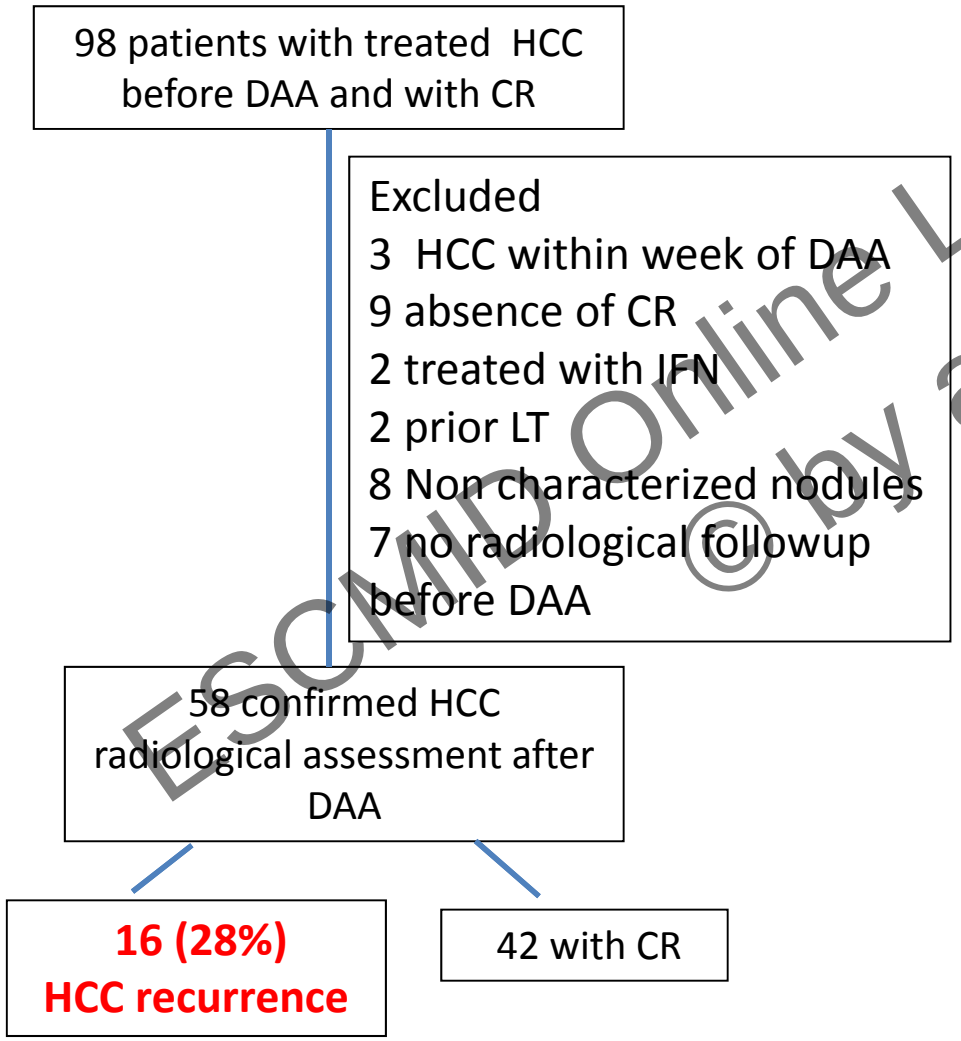
Study	Treatment	Negative End Point	Predictors
Saxena	SMV/SOF±RBV	Decompensation	T. bilirubin >1.3 mg/dL Any HE
Foster	LDV/SOF or DCV ± RBV	MELD worsening and/or serious adverse event	Age ≥65 years Albumin <3.5 g/dL Sodium <135
Belli	SOF/RBV, SOF/LDV, SOF/DCV	Lack of inactivation on the waiting list	Baseline MELD >16-20 Δ MELD @ 12wks Δ Albumin @ 12wks

Saxena V, et al. *Hepatology* 2015; Foster G, et al. *J Hepatol* 2016; Belli L, et al. *J Hepatol* 2016

Does DAA Therapy Increase the Risk of HCC Occurrence?

- **Few and mostly uncontrolled data**
- **Awaiting for ongoing prospective studies**

Does DAA Therapy Increase the Risk of HCC Recurrence?



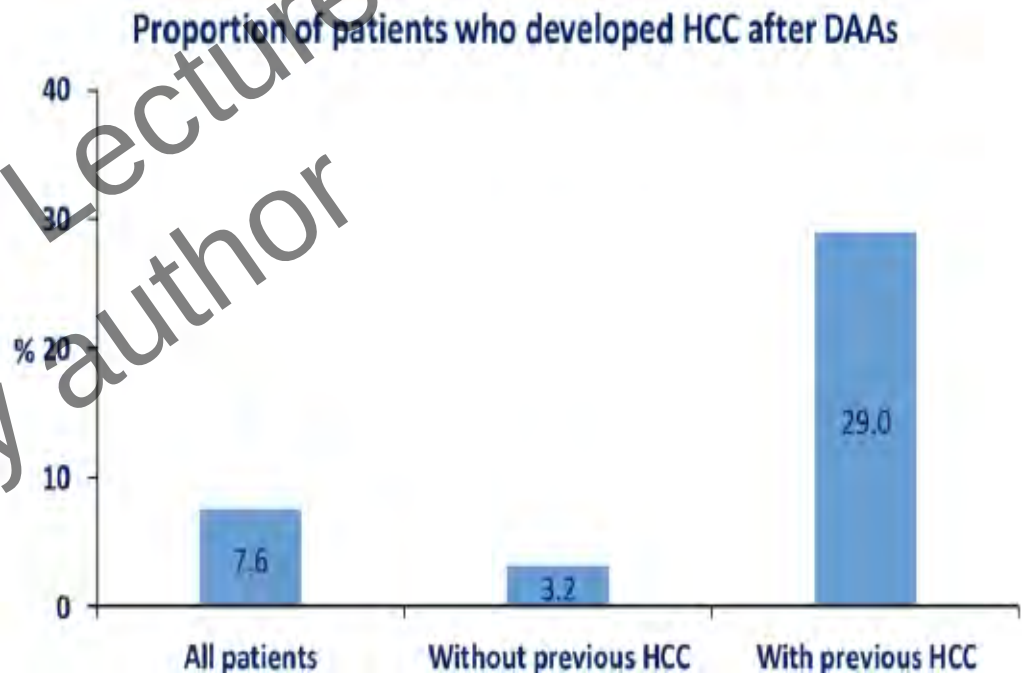
- 7/16 had been treated initially with resection and 9/16 with ablation
- Median time from HCC treatment to DAA was 11.2 m (25%-75%: 3.6-23.2)
- Median time from CR to recurrence was 3.5 months (1.1-8)
- Recurrence rate was higher than observed in historical non DAA treated controls

Reig et al. *J Hepatol* 2016;65:719-726.

HCC in DAA-Treated Patients

Baseline characteristics for the entire study population

Males, n. (%)	207 (60.2)
Age, yrs. (median, range)	63 (29-85)
HCV genotype, n. 1 / 4 2 / 3	 237 / 29 40 / 38
Antiviral Treatment, n. Naive Experienced	 153 191
Child-Pugh A / B, n.	305 / 39
Liver stiffness, Kpa (mean, SEM)	23.6 (0.8)
HBsAg positive, n. (%)	7 (2.0)
History of previous HCC, n. (%)	59 (17.2)



- **History of HCC, more advanced liver disease associated with the development of HCC after DAA therapy**

Conti F, et al. *J Hepatol* 2016;65:727-733.

HCC Recurrence After DAA Therapy

Cohort ANRS	N with HCC	N with HCC treated with DAA	HCC Recurrence Rate in DAA – treated group per 100 person-months	HCC Recurrence Rate in No-DAA group per 100 person-months
HEPATHER	**267**	**189**	**0.73**	**0.66**
CIRVIR	**79**	**13**	**1.11**	**1.73**
CUPILT (LT)	**314**	**314**	**3.1**	**--**

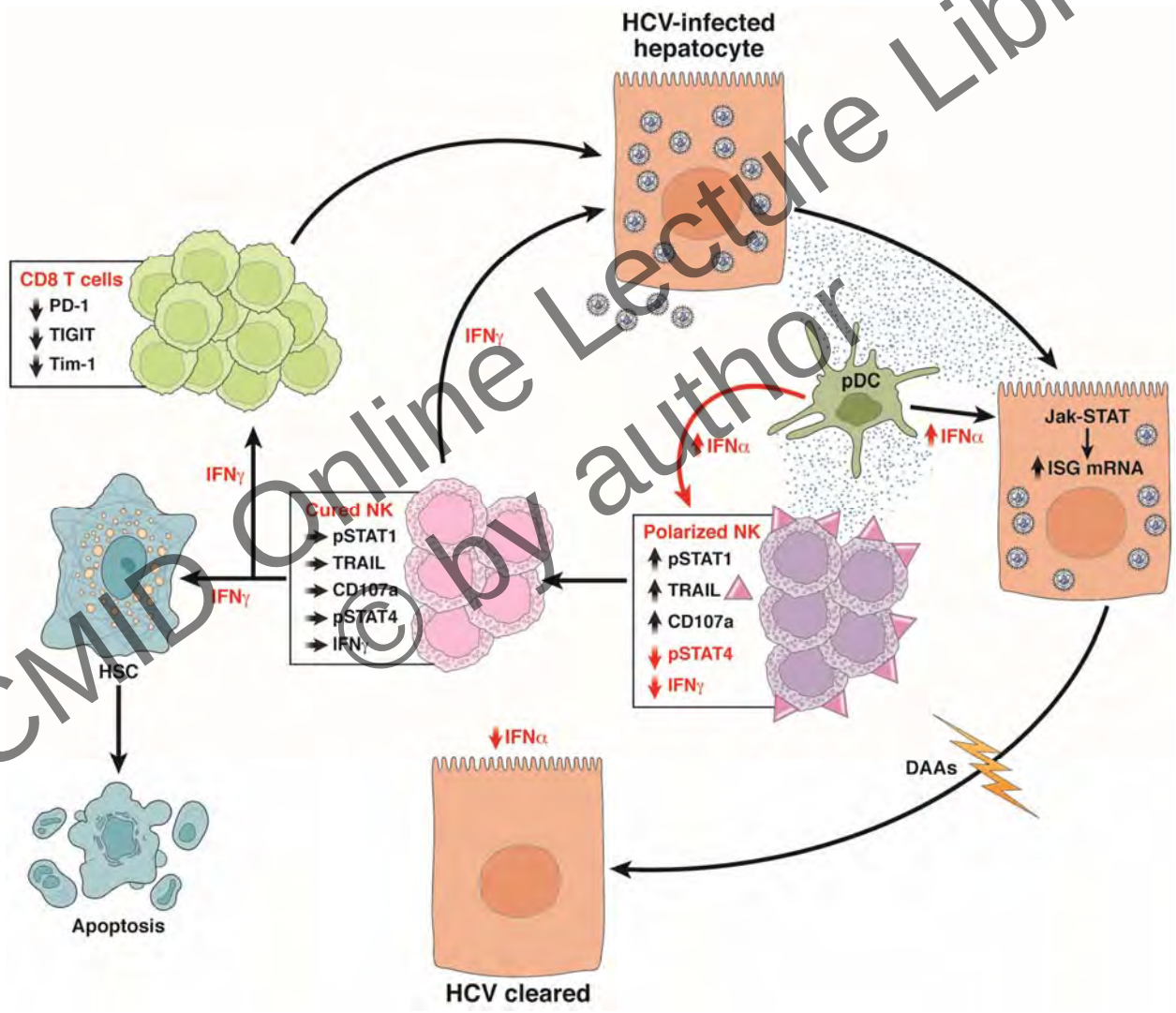
- All included patients had therapies with curative potential (resection, RFA, LT)
- **No evidence of increased risk of HCC recurrence in DAA-treated patients**

Pol S, *J Hepatol* 2016;65:734-740.

Interpretation of Discrepancies and Possible Pathogenetic Mechanisms

- 6-month recurrence rate suggests cancer cell dissemination rather than metachronous tumorigenesis.
- Selection bias due to wider DAA indications compared to IFNα-based therapies allowed us to treat very sick patients.
- DAAs induce a rapid normalization of the activated innate immune system (type I IFNs, NK cells) with possible loss of cancer immune surveillance.
- Clinical surveillance remains mandatory.
- Need of prospective studies but RCTs unethical.

DAAs Cure Innate Immunity in Chronic Hepatitis C



Serti E, et al. *Gastroenterology* 2015;149:190-200. Mondelli MU. *Gastroenterology* 2015;149:25–28.

Summary and Conclusions

- DAA treatment is safe and effective in compensated cirrhosis with hepatitis C.
- DAA treatment can be extended to marginally compensated or decompensated patients with favorable results.
- MELD, CTP and other parameters may predict outcome and incidence of SAEs.
- The association between DAA treatment and HCC appearance or reappearance is controversial and needs proper reassessment.