Treating HCV in Patients with Advanced Disease

Who Should We Treat? What is the "Point-of-No-Return"?

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Disclosures

- **Grants:** Gilead, BMS, AbbVie, Biotest, Eisai
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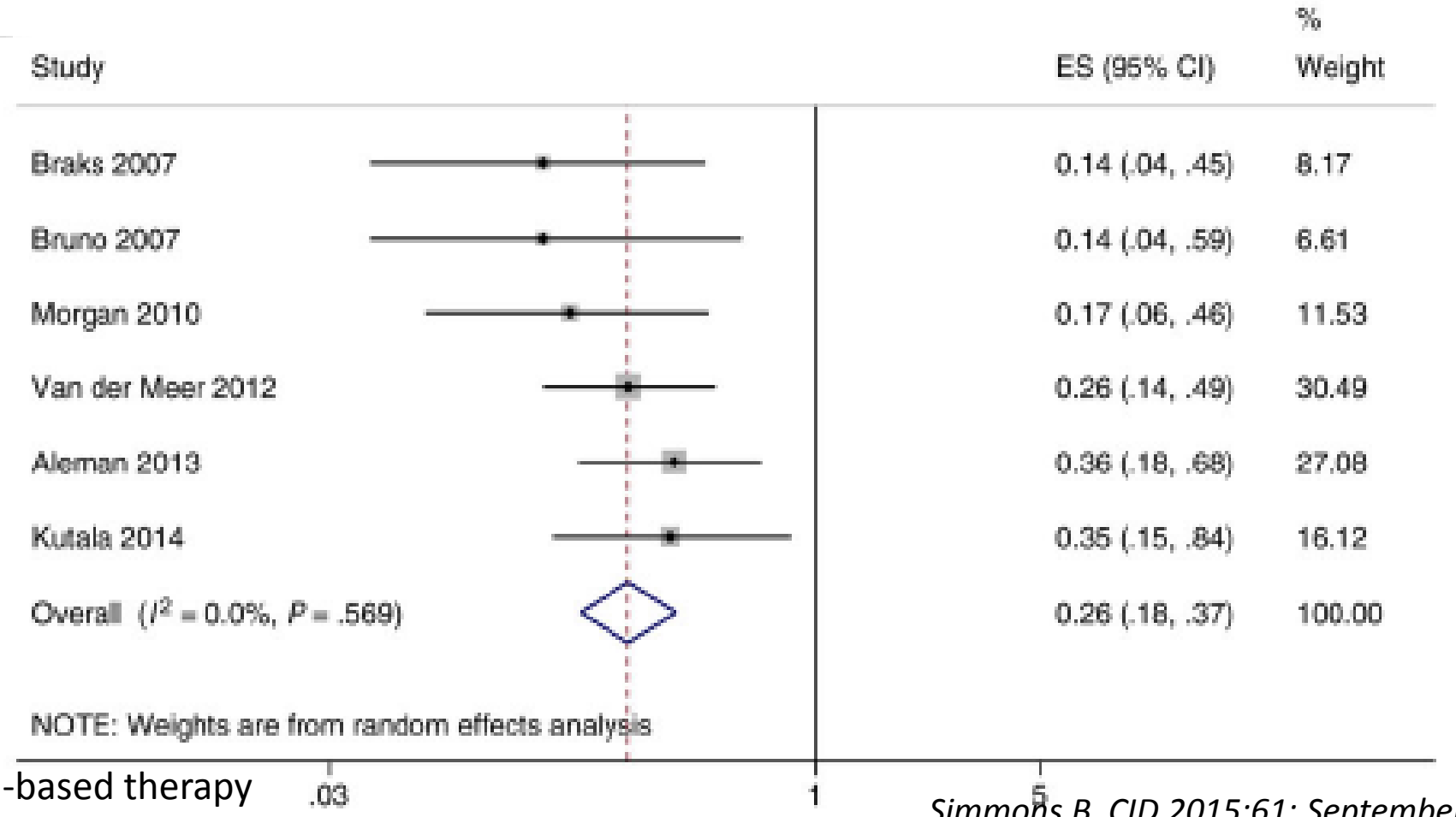
- **Royalties**: Up-to-Date

Key Aspects in Treating Patients with Advanced Disease

- **Vast majority of patients can achieve SVR**
  - **Though treatment options more limited if decompensated**
- **Treatment is well-tolerated and safe**
- **Most patients will derive important clinical benefits, including**
  - **Reduced risk of liver-related complications**
  - **Improve liver-related and overall survival**

75% Reduction in Mortality in Treated Patients with Compensated Cirrhosis

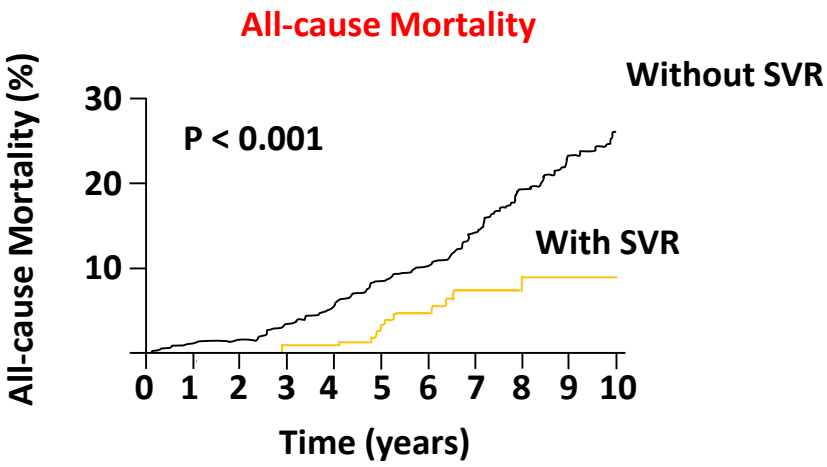
Meta-Analysis of those with SVR vs Non-SVR

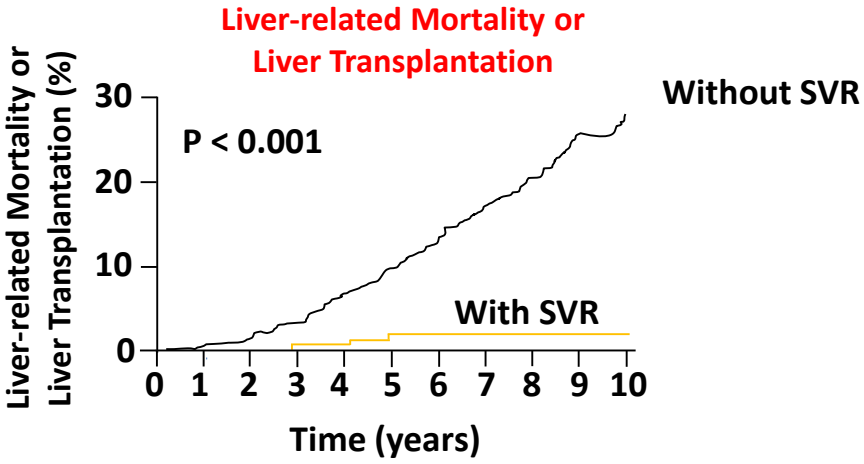


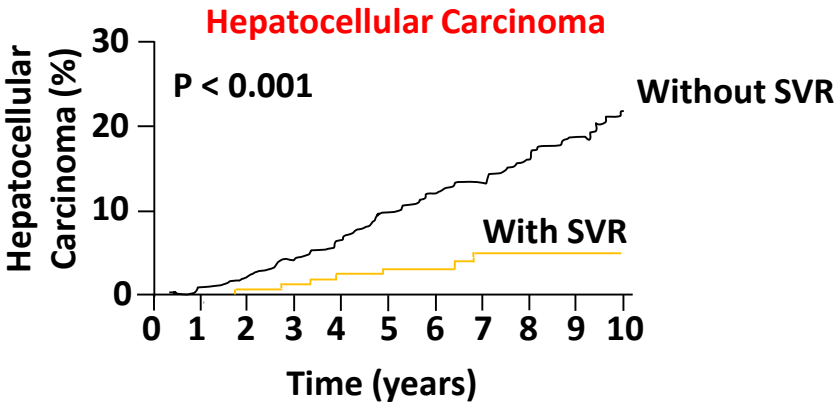
IFN-based therapy

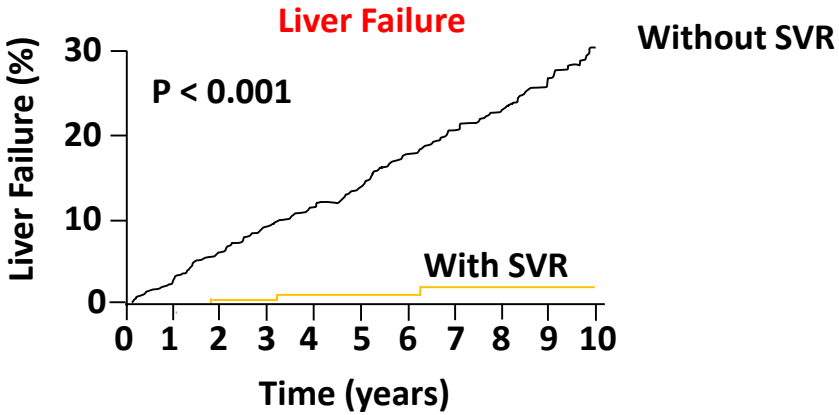
Simmons B, CID 2015;61; September 1

All-Cause Mortality Benefits in Patients with Advanced Disease by SVR Status









F3/4, Compensated

van der Meer AJ et al. *JAMA*. 2012;308(24):2584-2593.

Spectrum of Advanced Disease Identifying the Point of No Return

- Compensated cirrhosis
- Child-Pugh A
- MELD <10
- HCC as indication for LT

- Many DAA options
- Higher chance of SVR
- High chance of clinical benefits
- Cure before death likely

- Decompensated cirrhosis
- Child-Pugh B
- Less severe portal HT

- Fewer DAA options
- Slight reduction in SVR
- Cure before death likely
- Moderate chance of clinical benefits

- Decompensated cirrhosis
- Child-Pugh C
- Severe/refractory portal hypertensive complications

- Fewer DAA options
- Modest reduction in SVR
- Risk of dying before or with SVR
- Modest clinical benefits in short-term

Unique Aspects of Treating Patients with Decompensated Cirrhosis

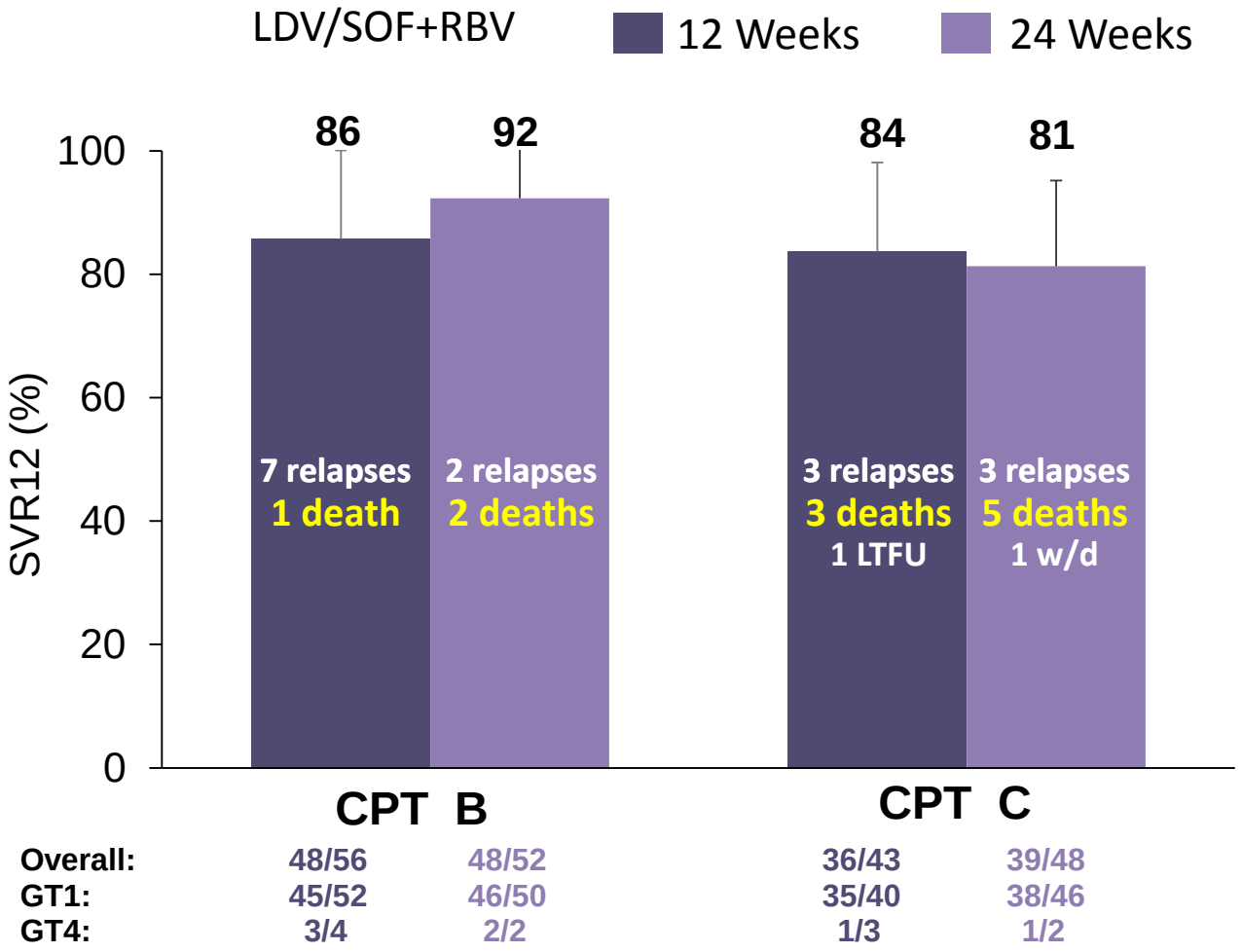
- SVR rates influenced by cirrhosis severity
  - CP-A (~95%) vs. CP-B/C (80-90%)
  - Tolerability and safety need closer scrutiny
  - Concurrent renal dysfunction may be present
- Consequences of treatment failure may be greater
- Concurrent consideration of impact of treatment on LT outcomes

Drug Options in Patients with Cirrhosis

DAA	Primary Metabolic Pathway	Suitable in Patients With Cirrhosis CP-A	CP-B	CP-C	Suitable if Renal Impairment
Sofosbuvir ± Ledipasvir	Renal	**Yes**	**Yes**	**Yes**	Not if CrCl < 30 mL/min
Daclatasvir	Hepatic	**Yes**	Yes	Yes	Yes, but not studied in dialysis
Simeprevir	Hepatic	**Yes**	(Yes)	No	Not if CrCl < 15 mL/min
Ombitasvir/Paritaprevir/r	Hepatic	**Yes**	No	No	Yes but not if dialysis
Dasabuvir	Hepatic	**Yes**	No	No	Yes but not if dialysis
Elbasvir/grazoprevir	Hepatic	**Yes**	No	No	Yes
Ribavirin	Renal	**Yes**	Yes	Yes	Yes, adjusted

Bifano M, et al. AASLD 2011. Abstract 1362. Garimella K, et al. Clin Pharm 2014. P43. Sofosbuvir [package insert]. Simeprevir [package insert]. Khatri A, et al. AASLD 2012. Abstract 758. German et al. AASLD 2013. Abstract 467. Kirby R, et al. 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy PO20

LDV-SOF + RBV for 12 Weeks is Effective Therapy for G1&4

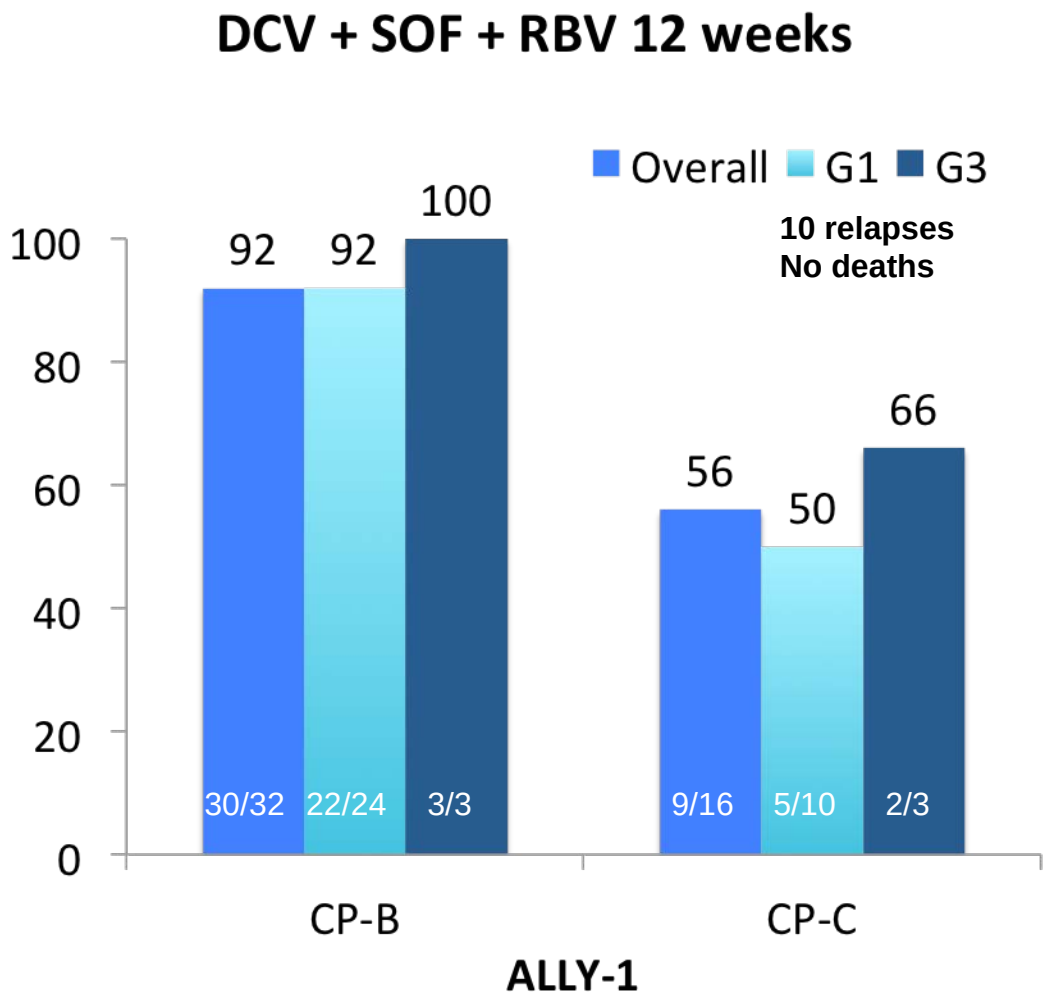


Analysis excluded 13 patients transplanted prior to posttreatment Week (FU) 12 with HCV RNA <LLOQ at last measurement prior to transplant, and 3 pretransplant patients who were CPT A at baseline. *Error bars* represent 95% confidence intervals (CIs).

Gane E, APASL 2016

SOF + DCV plus RBV for Decompensated Cirrhosis: ALLY-1

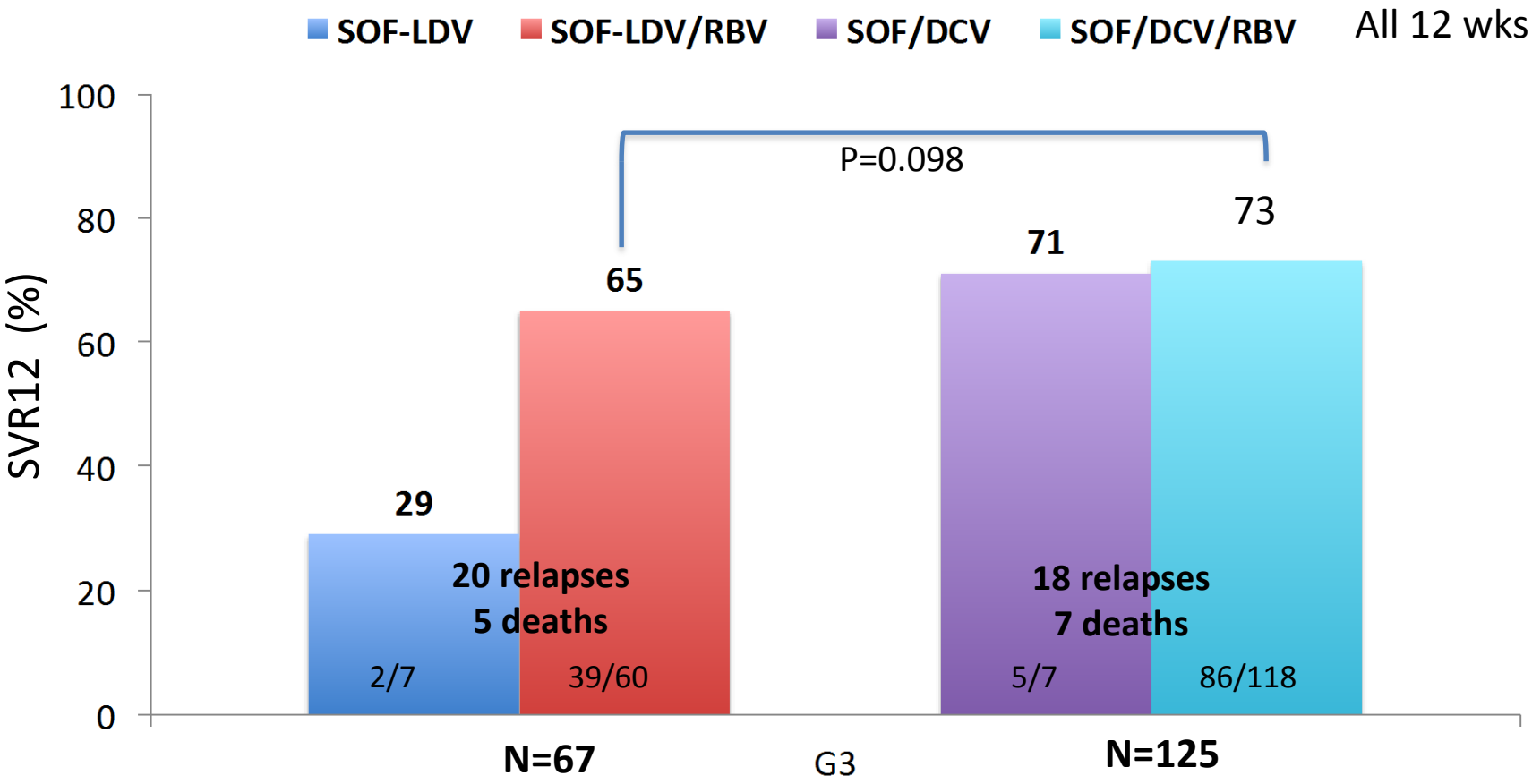
- N=48
- Child-Pugh Class
  - 67% CP-B
  - 33% CP-C
- G1-4 included (71% G1)
- 60% Rx experienced
- MELD range 8-27
  - 29% MELD >15
- Median RBV dose
  - 445 mg/day CP-B
  - 398 mg/day CP-C



Poordad F. *Hepatology*. 2016 Jan 11.

Efficacy of SOF plus NS5Ai in Decompensated Cirrhosis Genotype 3

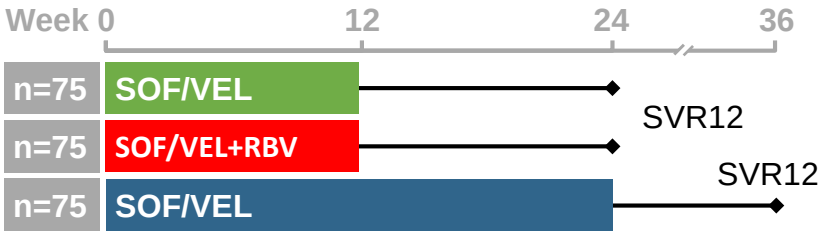
EAP UK



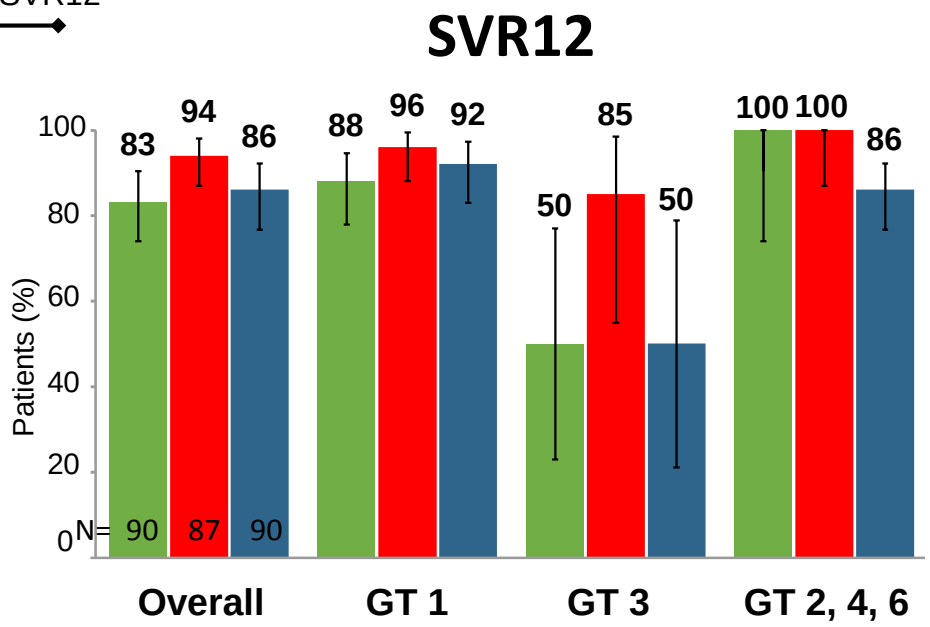
N=172 decompensated cirrhosis; N=14 LT, N=6 extrahepatic disease

Foster G, J Hepatol 2016, in press

Sofosbuvir/Velpatasvir for HCV Patients With Decompensated Liver Disease: ASTRAL-4



- **HCV GT 1-6 patients with <u>CPT B</u> cirrhosis**
- **Randomized to once daily, oral, FDC**
  SOF 400 mg/VEL 100 mg
  ± RBV



	GT1			GT3			GT2,4, 6		
Relapse	5	1	3	6	1	4			
VBT					1	1			
Death/LTFU	3	2	3	1		1			1

Charlton M, AASLD 2015: LB #13

What About Safety?

Serious AEs During Treatment with SOF + NS5Ai

	Number of events (% of total SAEs)	Number of patients (% of total population)
Total SAEs	175	119 (25.5%)
Likely related to liver disease and/or HCV therapy	138 (78.9%)	100 (21.4%)
Likely unrelated to liver disease and/or HCV therapy	37 (21.1%)	37 (7.9%)
Ascites	55 (31.4%)	38 (8.1%)
Hepatic encephalopathy	28 (16%)	23 (4.9%)
Variceal bleed	6 (3.4%)	6 (1.3%)
Infection	26 (14.9%)	23 (4.9%)
Liver transplantation	--	16 (3.4%)
New HCC	--	7 (1.5%)
Discontinuation of DAAs	--	42 (9%)
Deaths	--	14 (3.0%)

Foster G, J Hepatol 2016, in press

Safety of DAA Therapy in Patients with Decompensated Cirrhosis

- **Overall, DAAs appear to be safe and AEs consistent with clinical sequelae of advanced liver disease, RBV toxicity**
- **Ribavirin-associated anemia is common and more problematic to manage**
- **Difficult to determine if DAAs increases risk of adverse events as majority of studies are uncontrolled**
  - **In few controlled studies, AEs predicted by severity of liver disease and not treatment per se** *Saxena V, Hepatology, 2015*
- **Lactic acidosis occurred in 5/35 (14%) patients during therapy, while no event of lactic acidosis was observed prior to therapy** *Welker T J Hepatol 2016*

Who With Advanced Disease Should Be Treated?

Every patient with reasonably high chance of achieving SVR and surviving beyond SVR

Who With Advanced Disease Should NOT Be Treated?

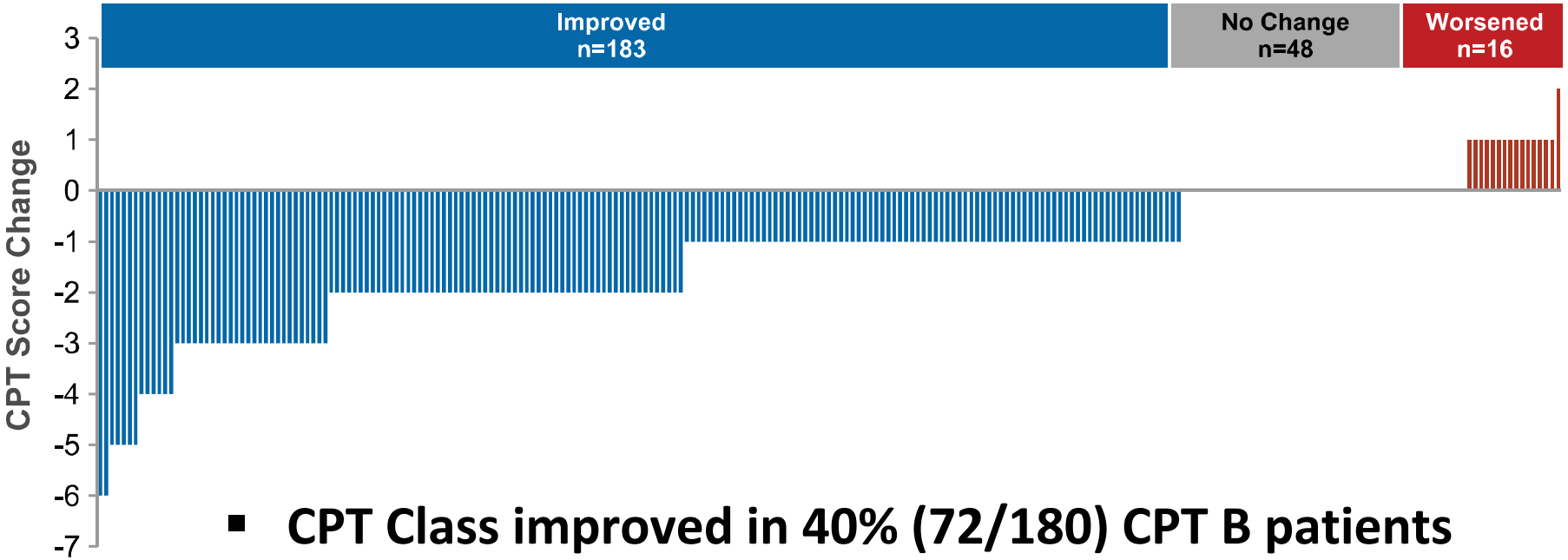
Patients without reasonably high chance of achieving SVR and surviving beyond SVR

- RBV ineligibility
- Prior NS5Ai failure
- High level resistance RAVs
- Renal failure
- Short time to LT

- Advanced HCC
- Other serious comorbidities
- Advanced decompensated cirrhosis: Child-Pugh C or "High" MELD

What is the Timeline for Improvement in Patients with Decompensated Cirrhosis?

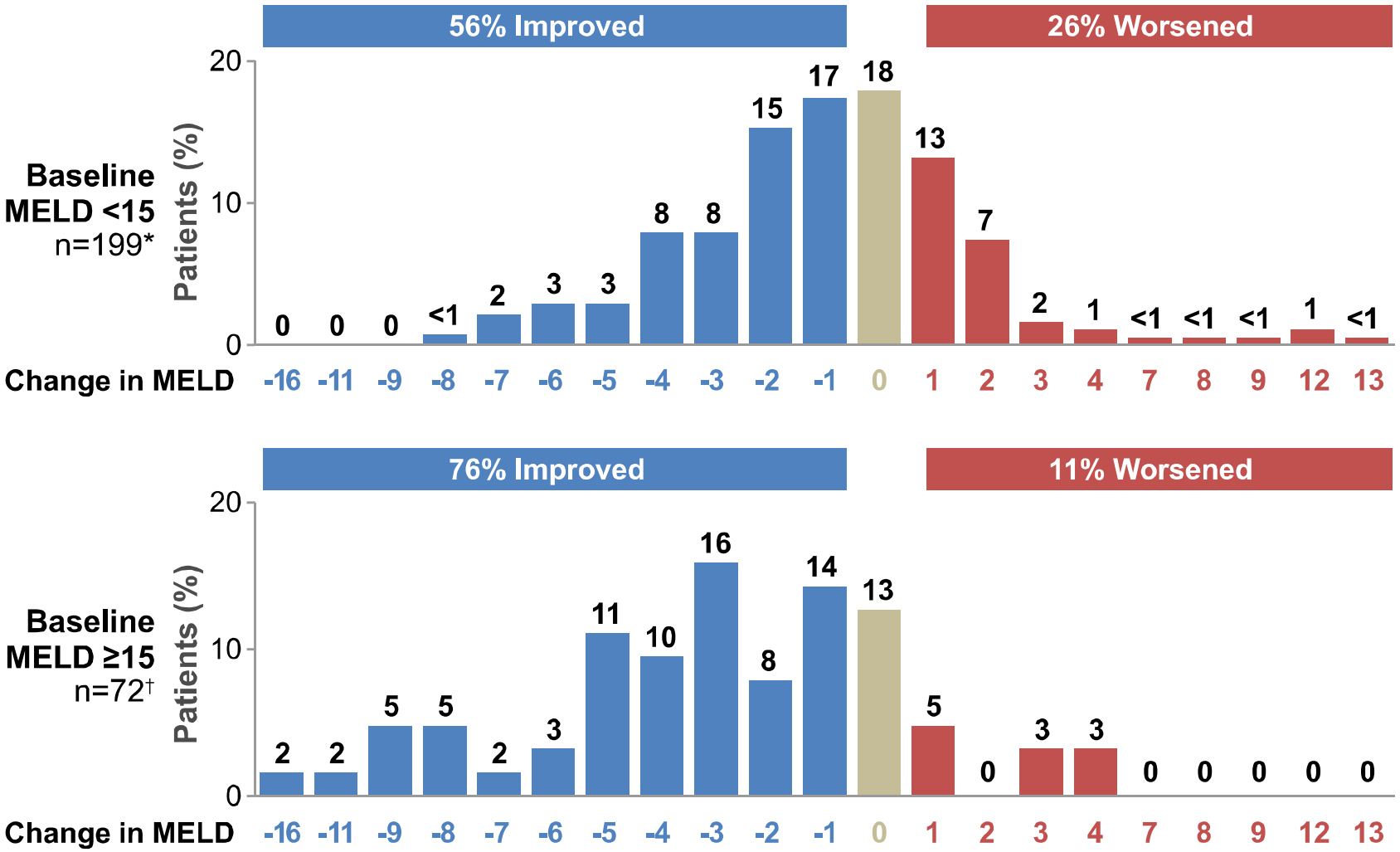
- 247 patients with decompensated cirrhosis who achieved SVR12
- CPT score change from baseline to 24 Weeks post-Cure in CPT B/C patients



- CPT Class improved in 40% (72/180) CPT B patients
- CPT Class improved in 76% (51/67) 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.

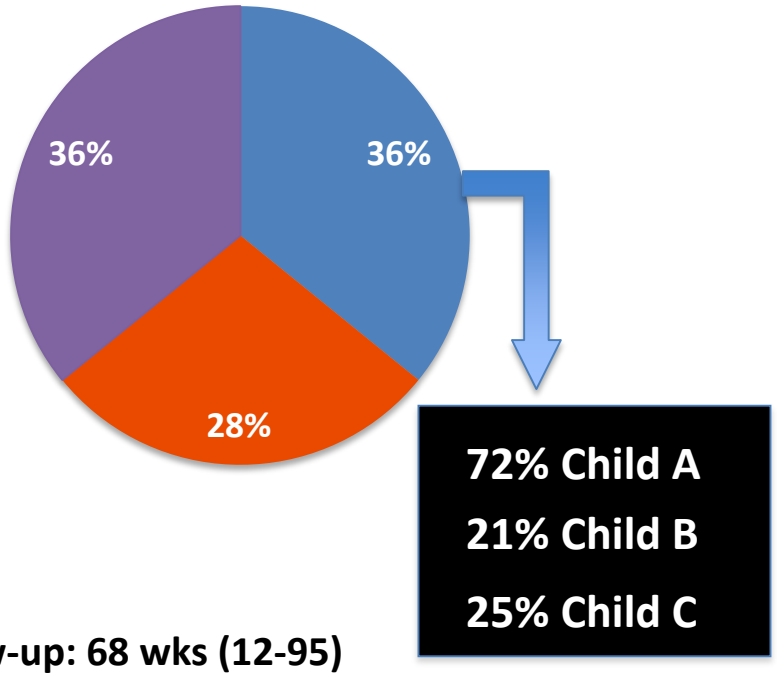
Gane E, APASL 2016

Clinical and Biochemical Responses in DAA Treated Patients on Waiting List (CPT A-C)

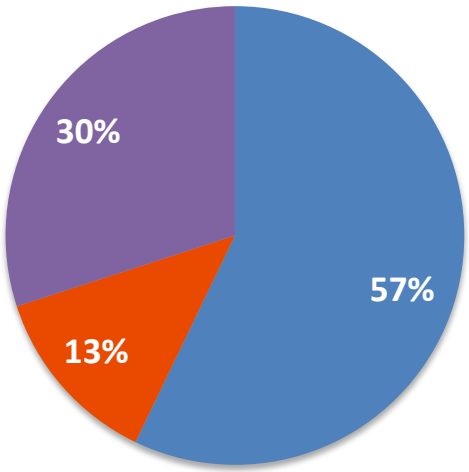
French multicenter cohort study

- **Complete response: Tbili <2, PT<1.2, albumin<3.5 + no ascites or HE**
- **Partial response: change in CP class**
- **No response**

Cirrhosis N=53



HCC N=70



Mean follow-up: 68 wks (12-95)

Coilly A, AASLD 2015, Abstract 95

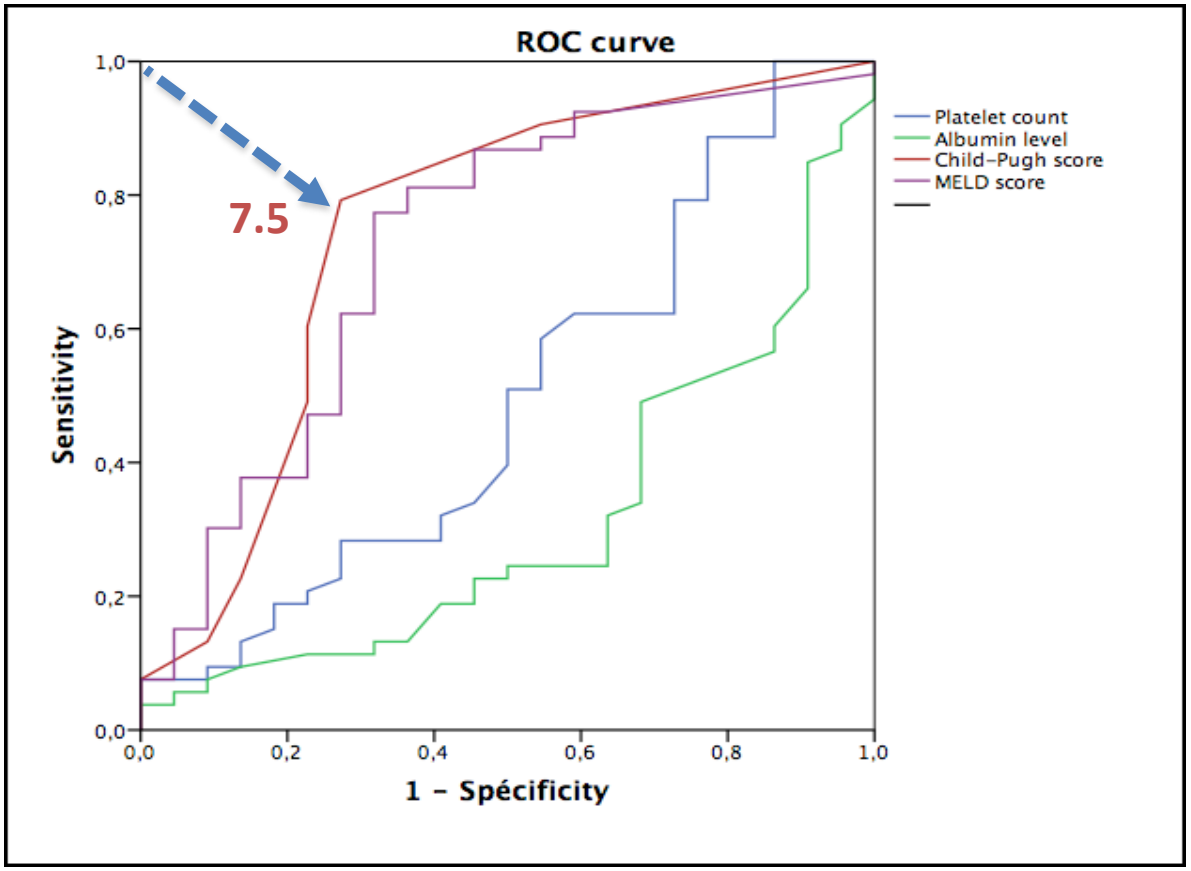
Improvement to Point of Delisting

Author, Region	Pascasio, Spain	Coilly, France
N with Cirrhosis	106	77
Median (range)MELD pre-treatment	13 (6-18)	12±5.2 (78% CP:B/C)
Duration follow-up post-treatment	--	68 weeks
% Delisted	**20%**	**18%**
% Improved (but not delisted)	--	16%

Coilly A, AASLD 2015, Abstract 95
Pascasio J, EASL 2016, Abstract FRI-464

Predicting Those Likely to Derive Complete Response

Complete response: Tbili <2, PT<1.2, albumin<3.5 + no ascites or HE



AUC for Child-Pugh score: 0.814

CPS better than MELD

Coilly A, AASLD 2015, Abstract 95

Can We Define Those at Risk of Harm During Treatment?

Study	Treatment	Harm Measured	Predictors
Saxena	SMV/SOF±RBV	Decompensation	Total bilirubin >1.3 mg/dL Any HE
Foster	LDV/SOF or DCV ± RBV	MELD worsening and/or serious adverse event	Age ≥65 years Albumin <35 mg/dL Sodium <135

Saxena V, Hepatology 2015
Foster G, J Hepatol 2016

Is there a "Point-of-No-Return"?

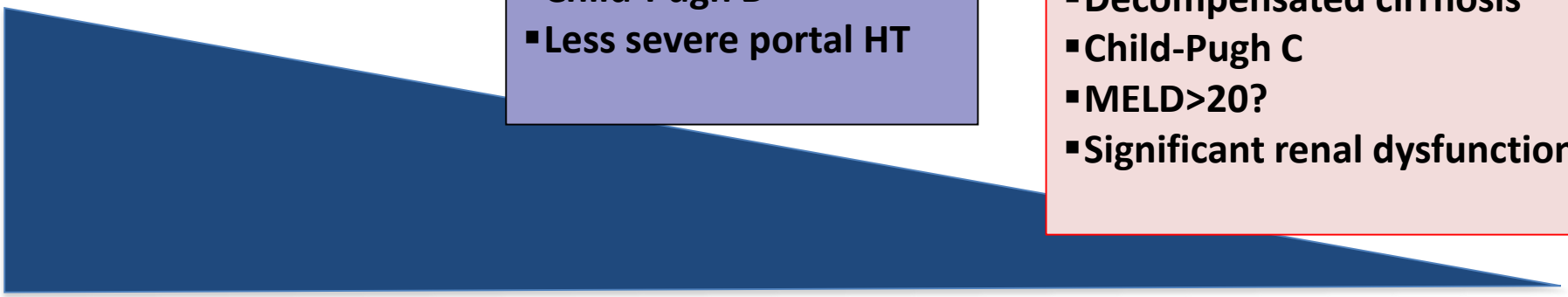
- **Probably** → **Insufficient time to improve**
  → **Inability to recovery/reverse**
- **Some clues:**
  - **Older age → regenerative capacity?**
  - **Significant portosystemic shunting?**
  - **Severity of liver synthetic dysfunction?**
- **Need better tools to assess regenerative/repair capacity**

Summary
Who Should We Treat?

- Compensated cirrhosis
- Child-Pugh A
- MELD <10

- Decompensated cirrhosis
- Child-Pugh B
- Less severe portal HT

- Decompensated cirrhosis
- Child-Pugh C
- MELD>20?
- Significant renal dysfunction



- Treat all patients

- Treat most patients
- Consider age, severity of PHT complications, severity of necroinflammation

- Don't treat unless LT is not an option and expected to survival at least 6 months