Issues with Liver Transplantation

Moderators: Pr D Samuel, Pr A Craxi

Speakers: Pr S Dharancy, Pr D Thabut

Mr Merc… L… O, 58 yrs-old

- Referred in our institution for refractory ascites to consider liver transplantation (March 2014)
- HCV-metabolic cirrhosis diagnosed in October 2013
  - Medical history
    - HCV infection, never treated (« normal ALT »)
    - Diabetes, arterial hypertension
    - Last upper endoscopy: grade 1 EV (January 2014)
    - Last US examination: dysmorphia, no nodule
    - Recently :
      - Admitted for fatigue, edema and tense ascites: 3 LVP in 6 weeks
  - Physical examination : T°: 36°9; BP: 108/65, 90/mn
    - Weight : 90kg/ 1m77 ;
    - Tense ascites, collaterals

Mr Merc… L… O, 58 yrs-old

- LFTs: Bilirubin=18/5 µmol/l, PT=67%, creatinin=78 µmol/l, INR=1.1, albumin=27 g/l
- Plt=101000/mm3
- Child-Pugh B9, MELD=8

- G1a HCV, PCRHCV=6 logUI/ml

- No contra-indication for LT, blood type O+

How would you manage this patient?

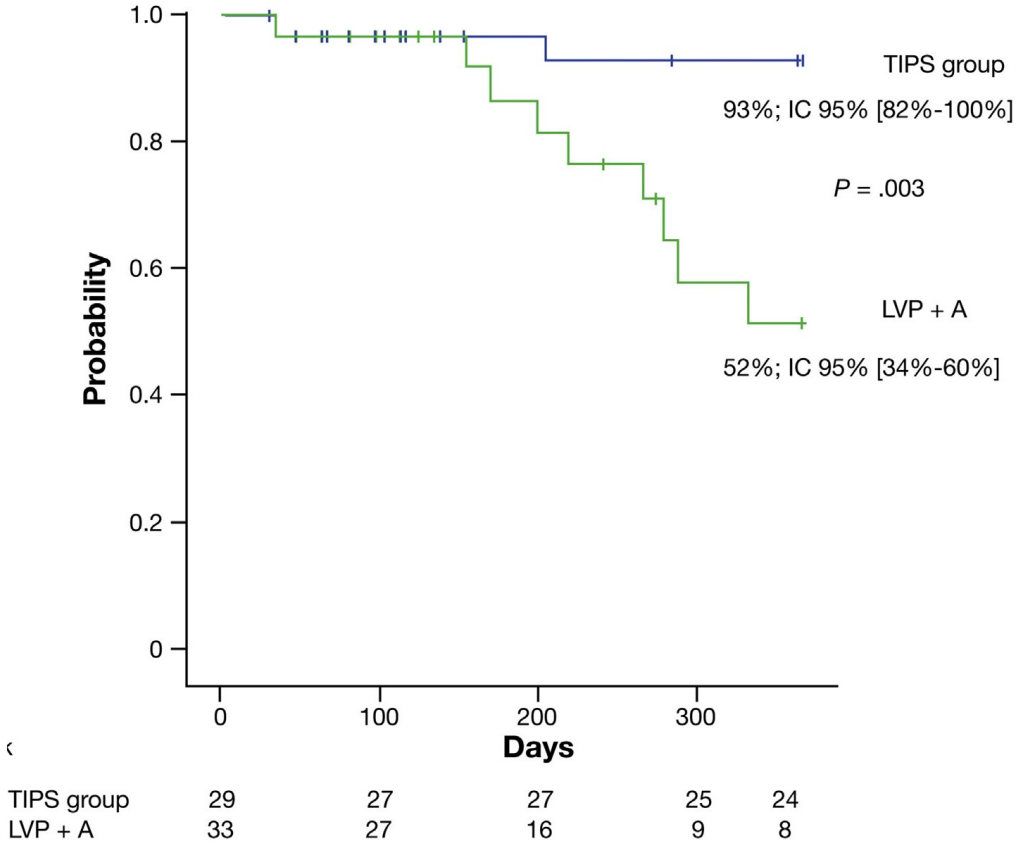
- Liver transplantation and HCV Tx after LT
- HCV Tx and then LT
- TIPS and then HCV Tx
- HCV Tx and then TIPS
- TIPS and then LT

How would you manage this patient?

- Liver transplantation and HCV Tx after LT
- HCV Tx and then LT
- **TIPS and then HCV Tx**
- **HCV Tx and then TIPS**
- TIPS and then LT

Covered TIPS in Pts with Refractory Ascites

Covered TIPS and transplant-free survival



- Plt>75000/mm3
- Total Bili<50 micromol/l

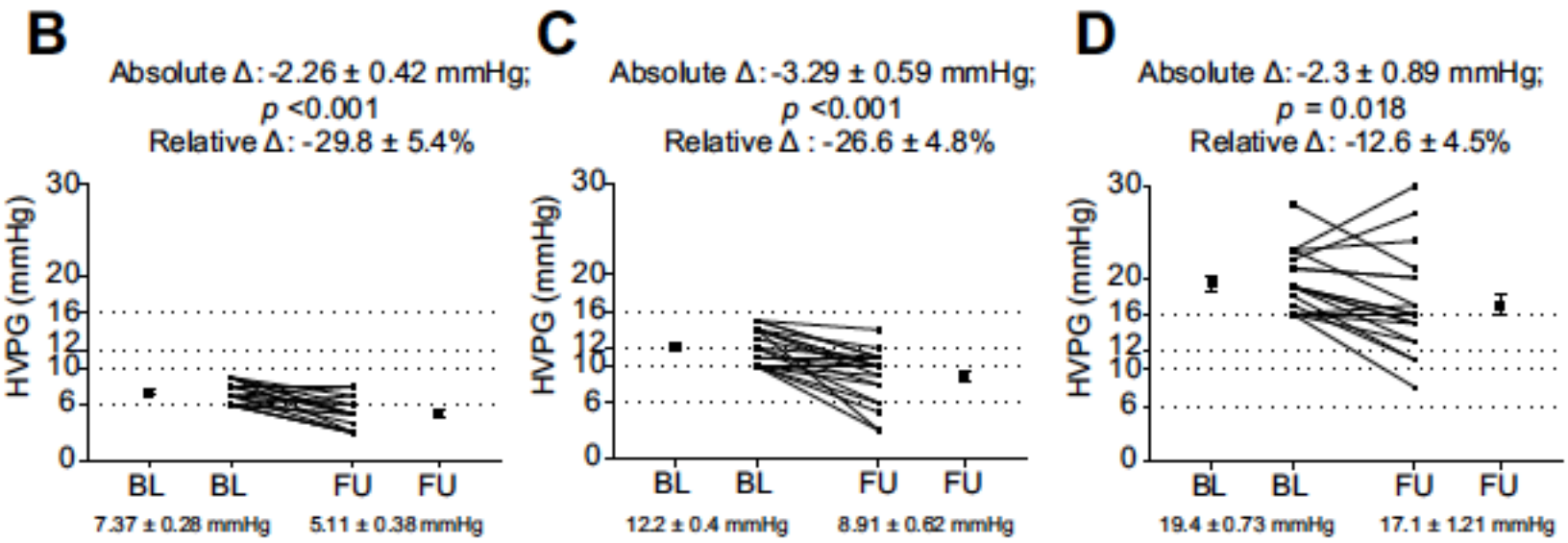
Bureau C et al., Gastroenterology 2017

Bureau C et al., J Hep 2011

Effects of HCV Therapy on HVPG

- 50 pts with viral C cirrhosis and PHT (HVPG] ≥ 6 mmHg); SVR 12=92% (DAAs)

HVPG variations



HVPG: 6-9 mmHg

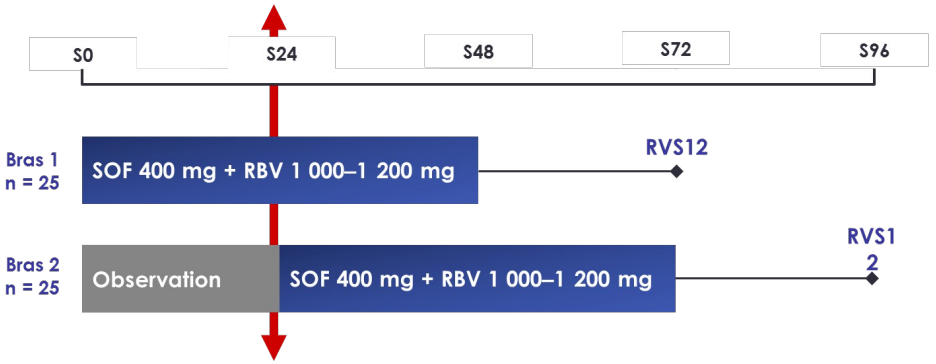
HVPG: 10-15 mmHg

HVPG > 15 mmHg

Mandorfer M, et al., J Hepatol 2016

Clinical effects of virosuppression on PHT

- 50 pts with « decompensated » cirrhosis Child-Pugh Aor B, HVPG> 6 mmHg,
- EV or gastric varices(78% pts with HVPG>12
- Median HVPG=16 mmHg=16)



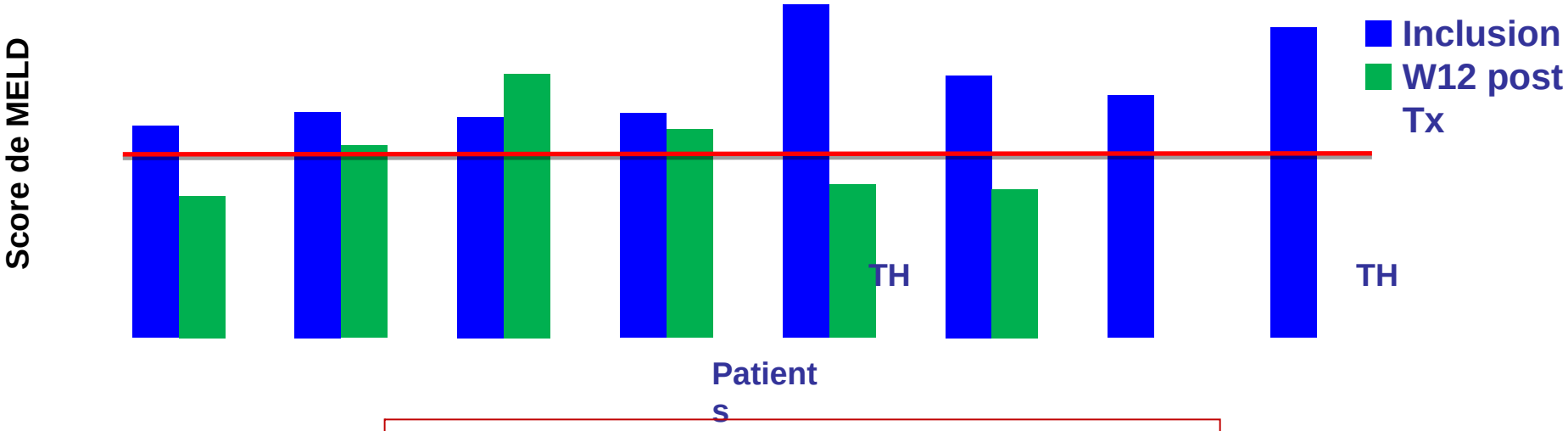
	Ascite		Encéphalopathie hépatique	
Patients , n	SOF + RBV (n = 25)	Observation (n = 25)	SOF + RBV (n = 25)	Observation (n = 25)
Initial	6	9	5	2
Semaine 12	5	8	3	3
Semaine 24	0	7	0	4

Afdhal N, EASL 2014

DAAs in Decompensated Pts ?

- 77 patients, decompensated cirrhosis, awaiting OLT (no CHC, MELD=12 ± 5 ; Child A (19 %), B (38 %)andt C (40 %)
- SOF/LDV +/- RBV or SOF/DCV +/- RBV or SOF/SMV +/- RBV
- SVR12 = 88 % ; Clinical and biochemical response: 31/72 patients (42 %)

Outcome of 8 patients with MELD ≥ 20 before treatment



Disappearance of ascites in 73% of cases
16 % of pts delisted for improvement

AASLD 2015, Coilly A et al., Abs. 95

Mr Merc… L… O, 58 yrs-old

- Referred 3 months after TIPS for discussion of HCV Tx

- Disappearance of ascites, no complication of TIPS
- Physical activity, improvment of nutritional status

- Child B7, MELD=7

How would you manage this patient?

- The patient should be listed for LT and treated for HCV after LT
- The patient should be treated for HCV without being listed for LT
- The patient can be treated by Sofosbuvir-Velpatasvir
- The use of RBV is mandatory in case of HCV Tx because of cirrhosis
- Protease inhibitors is contra-indicated in pts with history of decompensated cirrhosis

How would you manage this patient?

- The patient should be listed for LT and treated for HCV after LT
- **The patient should be treated for HCV without being listed for LT**
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- **Protease inhibitors are contra-indicated in pts with history of decompensated cirrhosis ?**

Clinical effects of virosuppression on liver function

- ATU DCV in France
- 72 Pts Child B or C
- SOF + DCV ± RBV

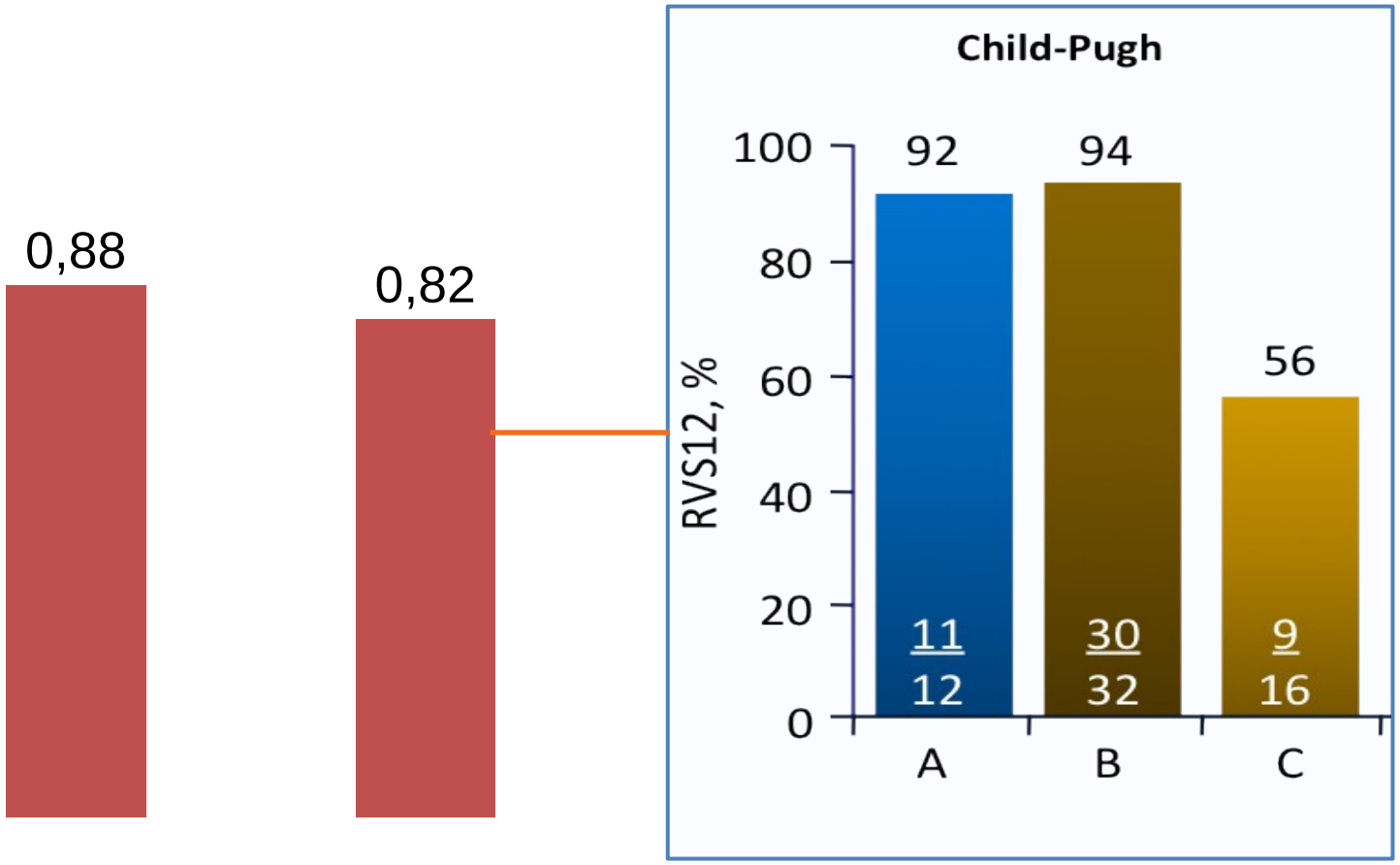
Improvement **Aggravation** **No change**

Child-Pugh at Baseline	Child-Pugh class at SVR12, n (%)		
	A	**B**	**C**
B	**40 (56)**	**19 (26)**	**3 (4)a**
C	**3 (4)**	**6 (8)**	**1 (1)b**

- Improvement of Child-Pugh class in 68% of patients (49/72)
- Only a minor proportion go from Child C to Child A

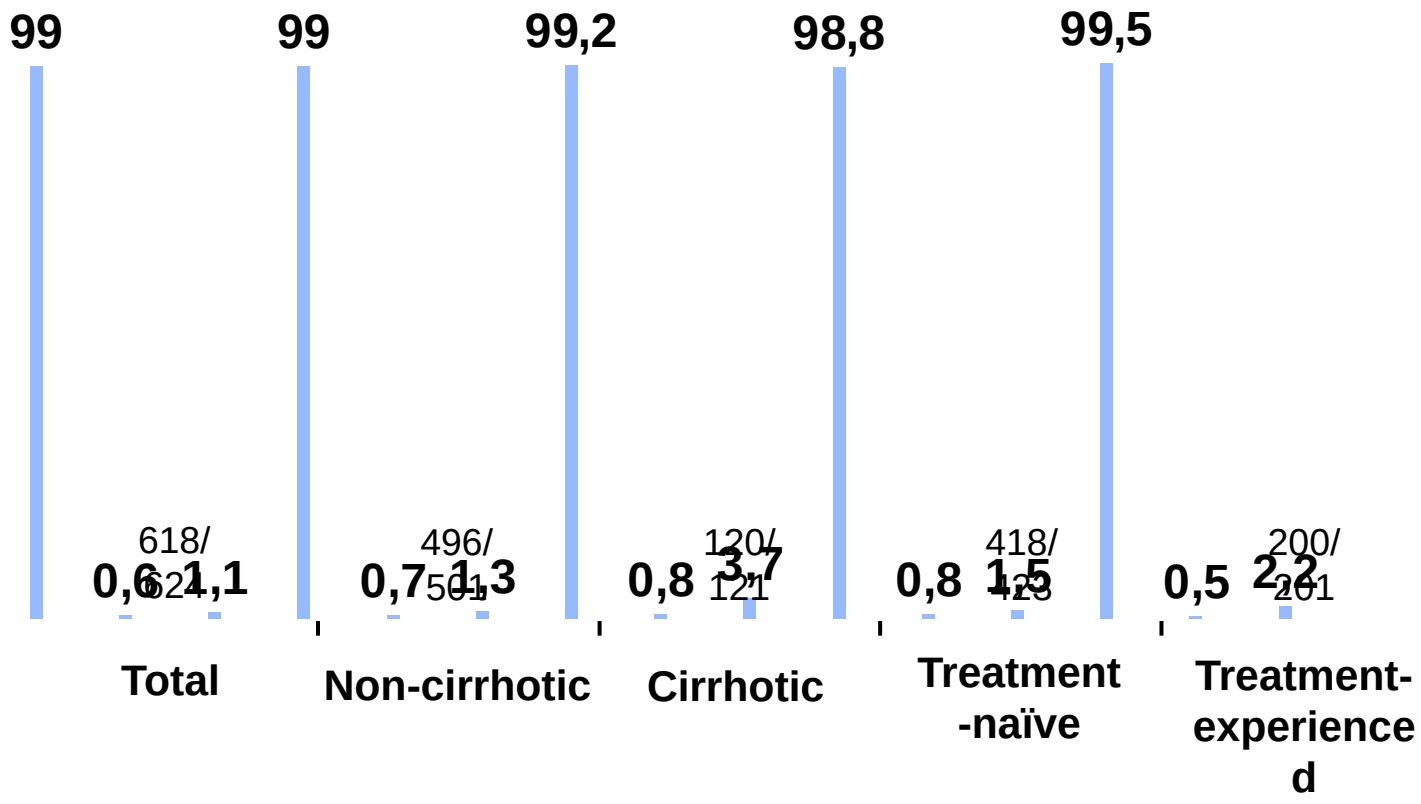
Leroy et al., JFHOD 2016

Efficacy of DAAs in patients with compensated cirrhosis



(1) Charlton M. Gastroenterology 2015; (2) Poordad F, Etats-Unis, EASL 2015, Abs. L08;

ASTRAL-1: SOF/VEL for 12 weeks is effective regardless of cirrhosis and treatment experience



Feld JJ, et al. N Engl J Med 2015

3D + RBV in Child B patients

➔ ***Phase IIIb study, G1a et G1b, n=11, SVR=100%***

➔ ***Side effects in 5 patients, decompensation, hyperbilirubinémia and anemia***

➔ *3D + RBV treatment is effective in Child B patients but side effects are frequent and severe*

➢ Protease inhibitors are contra-indicated in Child C pts

AASLD 2015, Mantry PS et al., abstr. P72

Mr Merc… L… O, 58 yrs-old

- Lost of follow-up, never treated for HCV
- Referred again in February 2017 because of jaundice, psychomotor slowering, fatigue, in order to discuss LT
- LFTs: Bilirubin=101/73 µmol/l, PT=35%, creatinin=97 µmol/l, INR=2.1, albumin=29 g/l
- Child-Pugh C11, MELD=22
- No contra-indication for LT, blood type O+

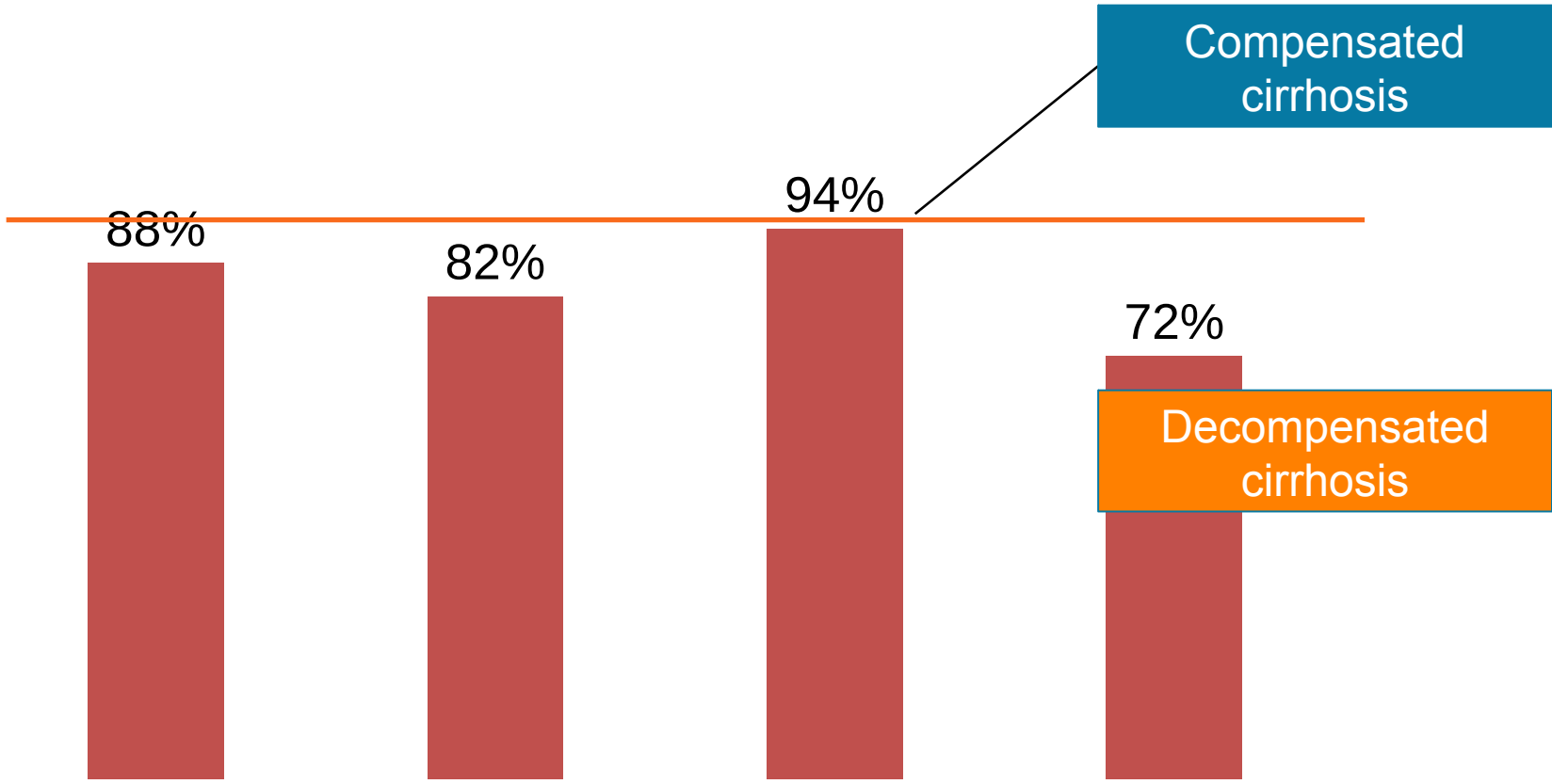
How would you manage this patient?

- Listing for LT and no HCV Tx because of little efficacy of HCV Tx in decompensated patients
- Listing for LT and no HCV Tx because of contra-indication to DAAs in decompensated patients
- Listing for LT and no HCV Tx because of low probability to have a MELD<15 after Tx
- Listing for LT and HCV Tx to decrease mortality on waiting-list
- HCV Tx before listing because of the risk of graft reinfection

How would you manage this patient?

- Listing for LT and no HCV Tx because of little efficacy of HCV Tx in decompensated patients
- Listing for LT and no HCV Tx because of contra-indication to DAAs in decompensated patients
- **Listing for LT and no HCV Tx because of low probability to have a MELD<15 after Tx ?**
- **Listing for LT and HCV Tx to decrease mortality on waiting-list ?**
- HCV Tx before listing because of the risk of graft reinfection

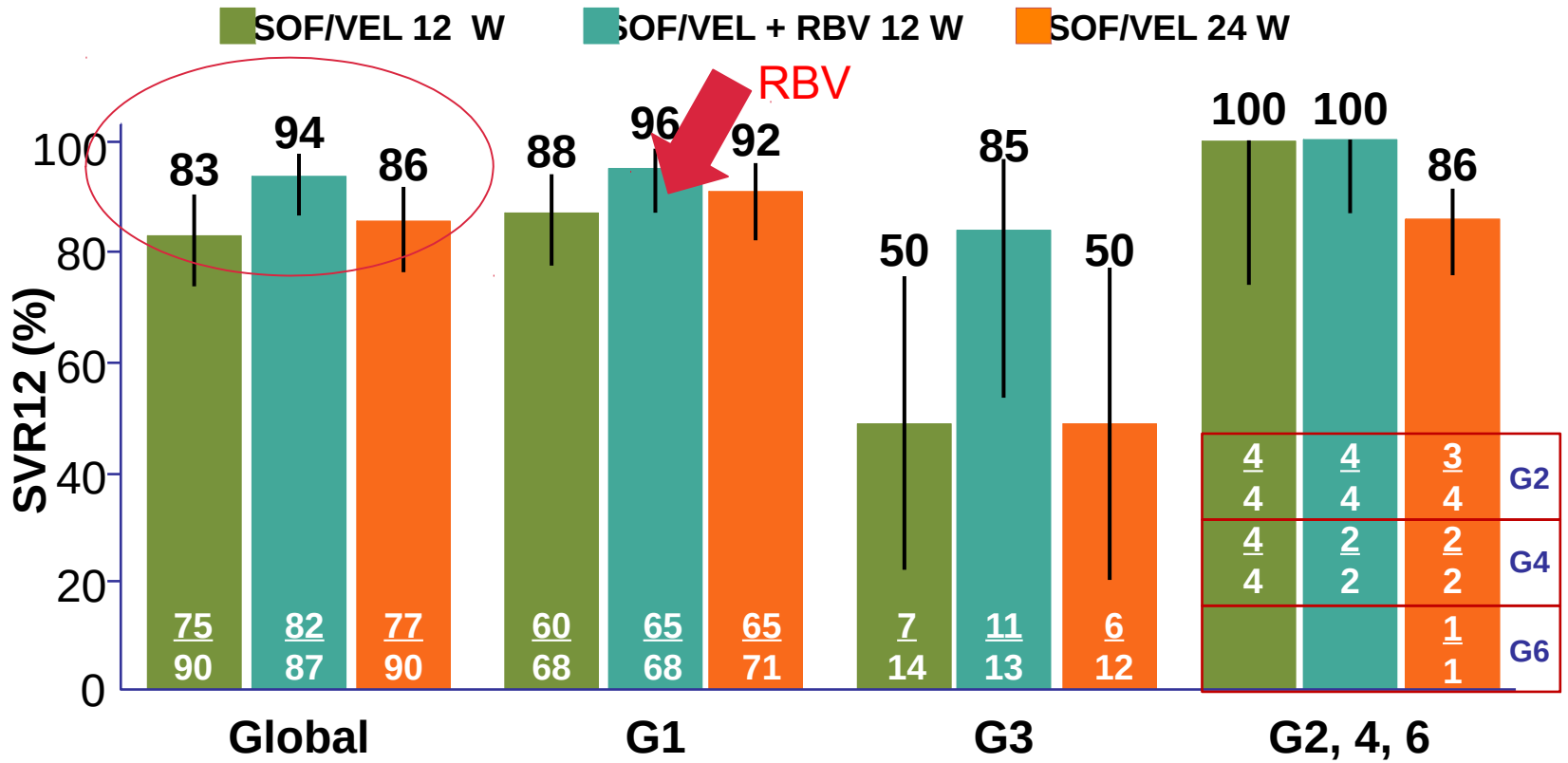
Efficacy of DAAs in cirrhotic patients



(1) Charlton M. Gastroenterology 2015; (2) Poordad F, Hepatology 2016 Abs. L08; (3) Poordad F NEJM 2014 (4) Saxena V, Hepatology 2015

New generation of DAAs in Child B cirrhotic patients

ASTRAL 4 : sofosbuvir/velpatasvir

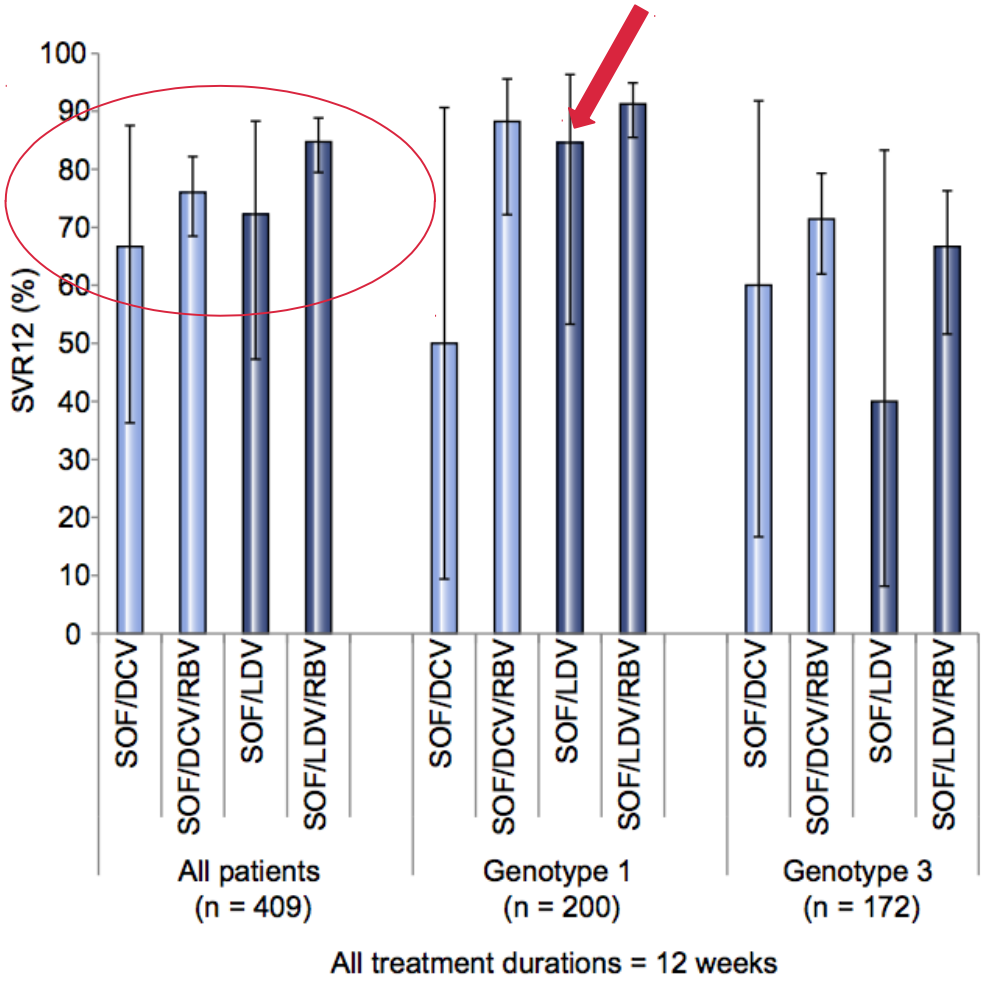


- SVR 85%, RBV, 24 sem not better

Curry et al. N Engl J Med. 2015

Efficacy of DAAs in patients with decompensated cirrhosis

- Early Access Program UK
- 409 pts with decomlpensated cirrhosis Child >B7
- Sof, Dcv, Ldv 12 sem
- SVR: 91% G1, 68% G3



- Efficacy < other pts
- 12 sem with RBV
- Pb of GT3

Foster J. J Hepatol. 2016

Safety in severe patients

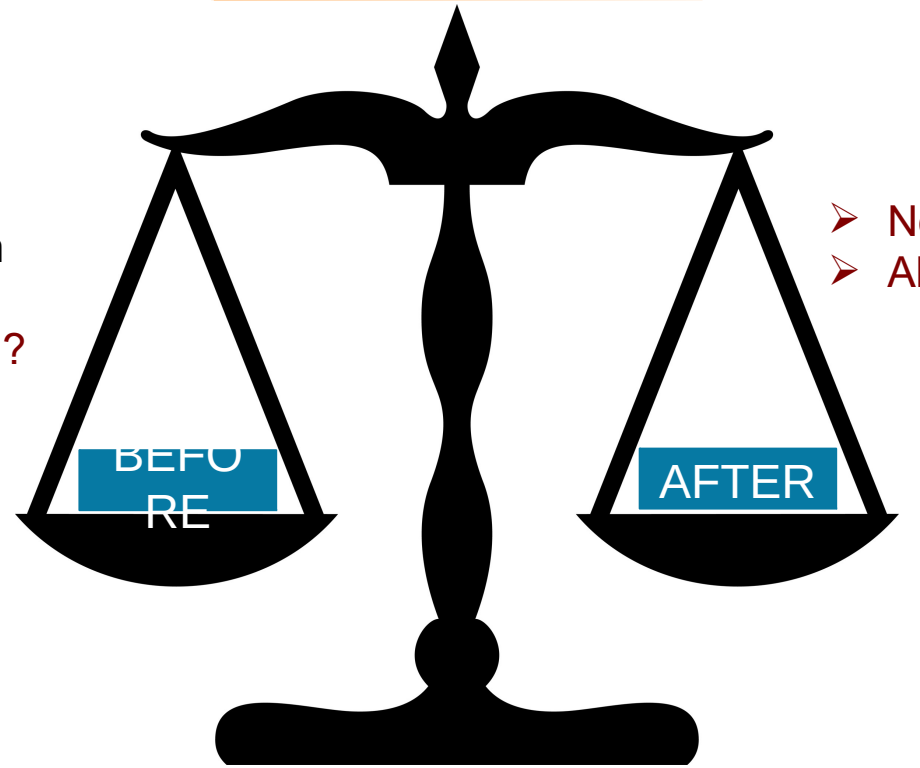
Pharmacokinetics of DAAS				
	Hepatic function impairment			Avoid
	Mild	Moderate	Severe	➢ 24% AE, related to RBV
Simeprevir1		+ 2.44	+ 5.22	Child C
Sofosbuvir2		+ 1.26	+ 1.43	
Ledipasvir3	No adjustement			
Paritaprevir/r4	- 0.71	+ 1.62	+ 10.23	Child C
Ombitasvir4	+ 0.92	+ 0.70	+ 0.45	
Dasabuvir4	+ 1.17	+ 0.84	+ 4.19	Child C?
Asunaprevir5	- 0.79	+ 9.8	+ 32	Child B/C
Daclatasvir5	- 0.57	- 0.62	- 0.64	

1. Ouwerkerk-Mahadeva S, et al. AASLD 2013. Oral #65; 2. Gilead Sciences Europe. SOVALDI (sofosbuvir), Summary of Product Characteristics, January 2014; 3. German P, et al. AASLD. 2013. Oral #52; 4. Khatri A, et al. AASLD. 2012. Oral #66; 5. Bifano M, et al. AASLD. 2011. Oral #78.

DAAs in most severe patients

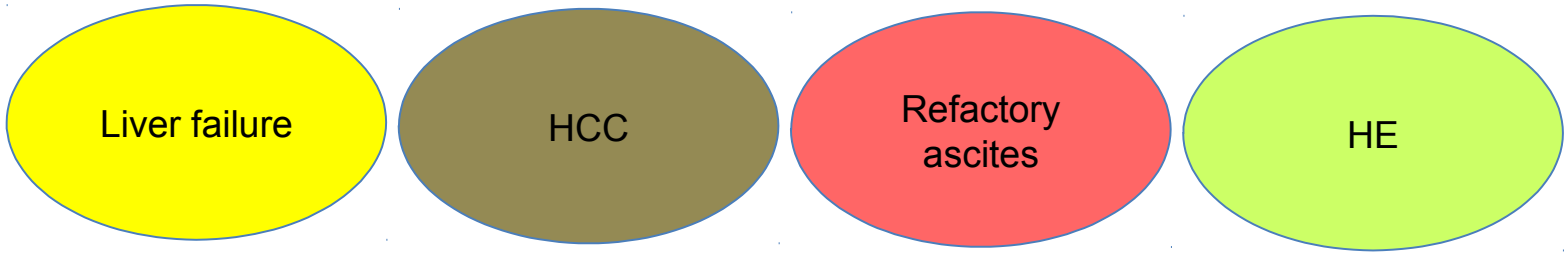
- DAAs and decompensated cirrhosis
  - Good efficacy, inferior to non decompensated pts
  - RBV is mandatory
  - Safety OK
  - No PI (new DAAs)

DAAs era

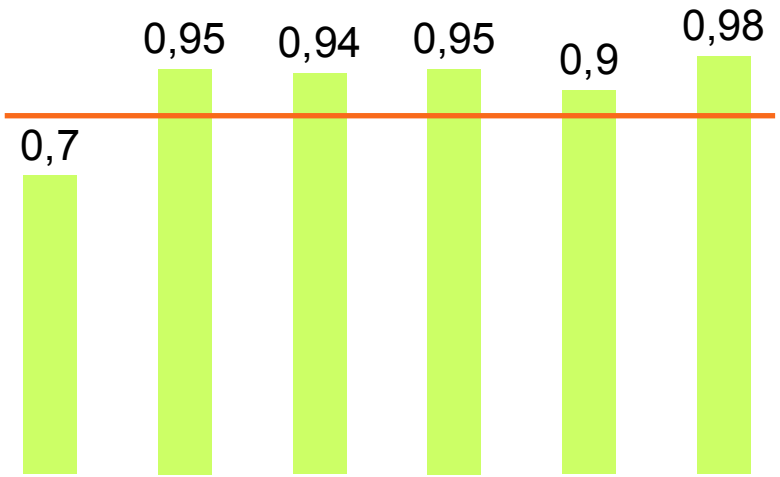


- Avoid graft reinfection
- Avoid transmission
- Avoid transplantation ?

- Not avoid accesibility to LT
- Allow use of HCV+ livers



DAAs after LT



	Ciclosporine	Tacrolimus
Sofosbuvir	◆	◆
Sofosbuvir/Ledipasvir	■	■
Velpatasvir Daclastavir	◆	◆
Simeprevir	●	■
Ombitasvir, paritaprevir, ritonavir, dasabuvir	■	■
Grazoprevir, Elbasvir	■	■

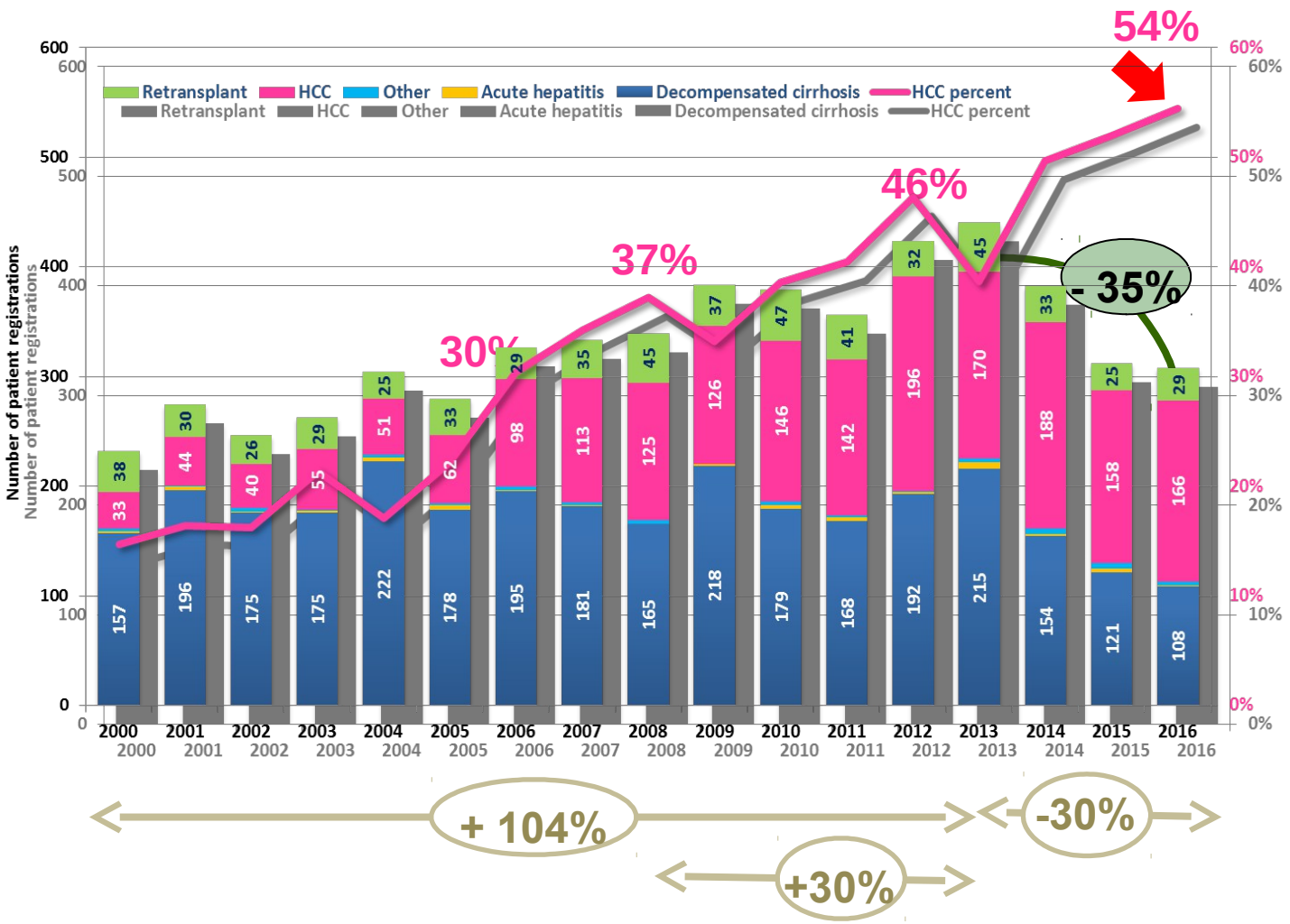
- Ttt efficacy (SVR>90%)
- Few side effects

Effect of DAAs on LT listing in HCV+ patients: the French Experience

Decrease of 30% of listed pts in 3 years

HCC: main indication of listing in 2016

Decrease of 35% of listing for retransplantation



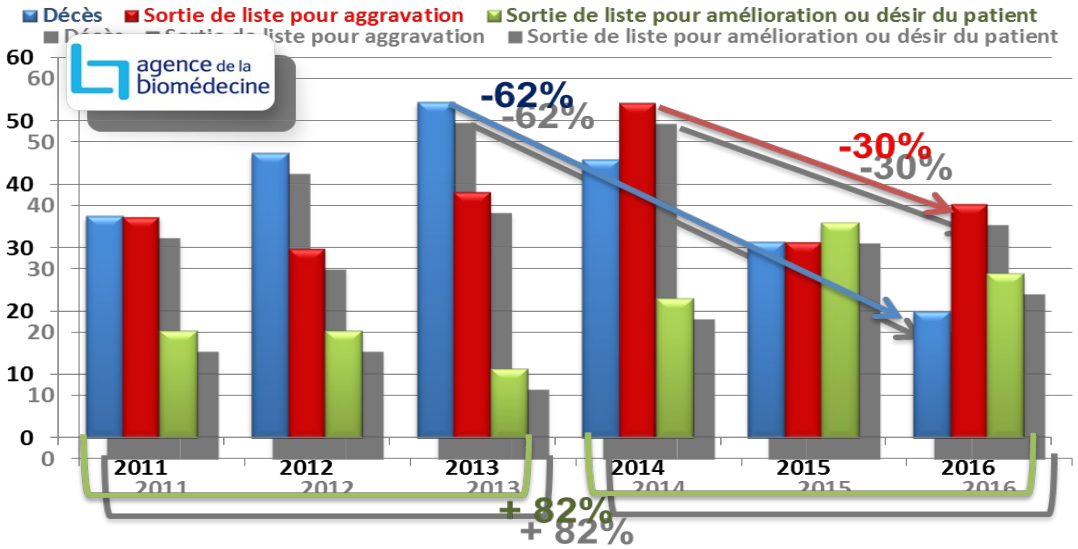
Effect of DAAs on LT listing in HCV+ patients: the French Experience

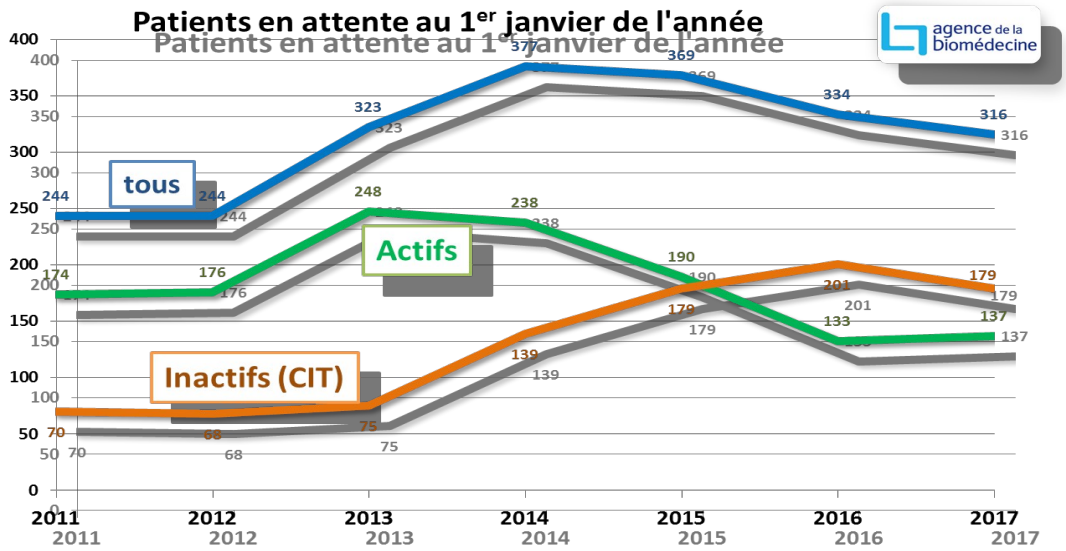
Decrease of mortality on waiting-list of **62%**

Decrease of **30%** of drop-out for aggravation

Increase of **82%** of delisting for improvement [2011 -2013] vs [2014 - 2016]

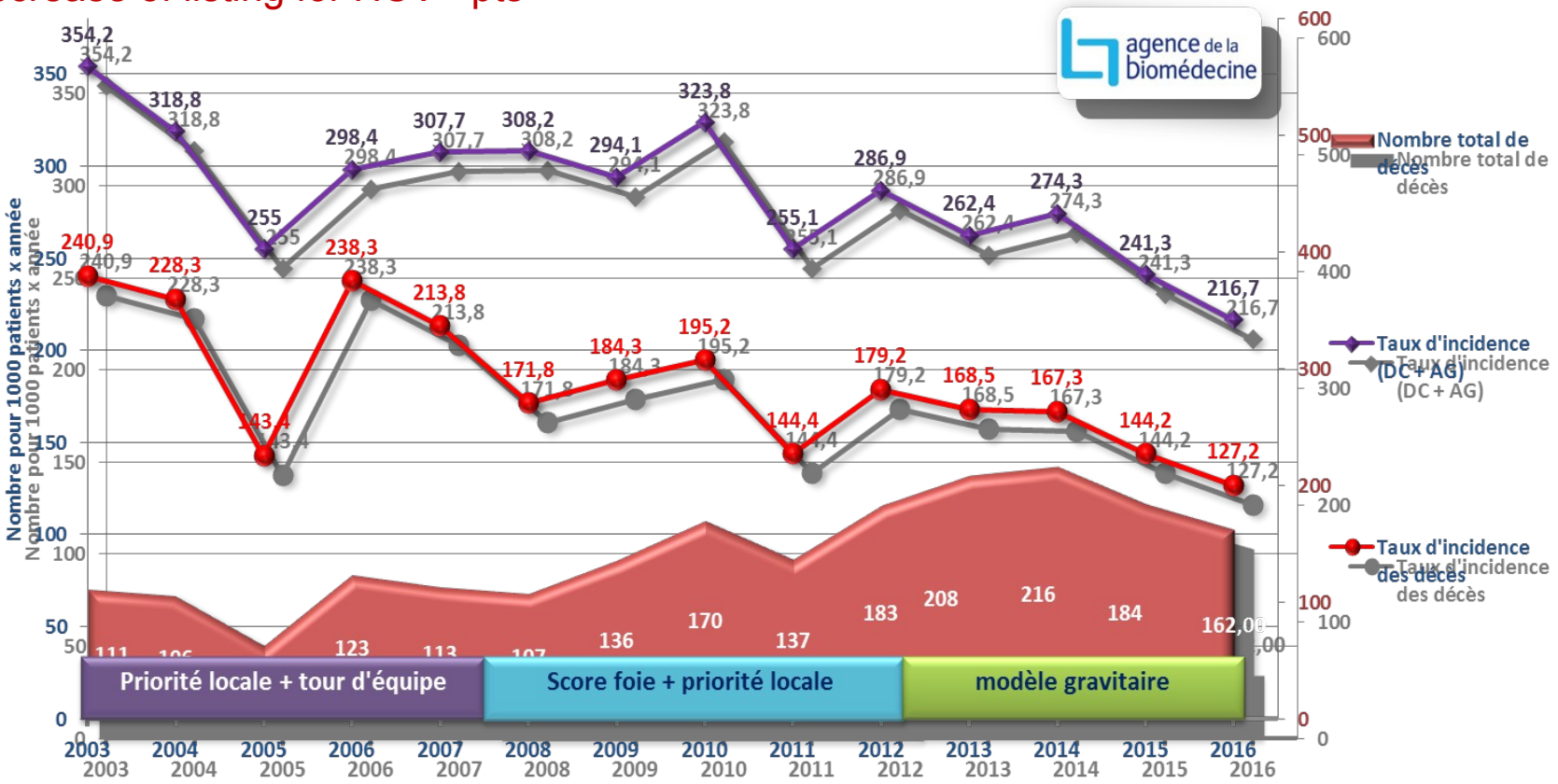
Increase of Pts inactivated (for improvement) 23% (2013) → 60% (2016)





Decrease of Mortality and Drop-out for all indications of LT in France

Observed despite an increased incidence of listing
Redistribution of grafts towards HCV- pts
Decrease of listing for HCV+ pts

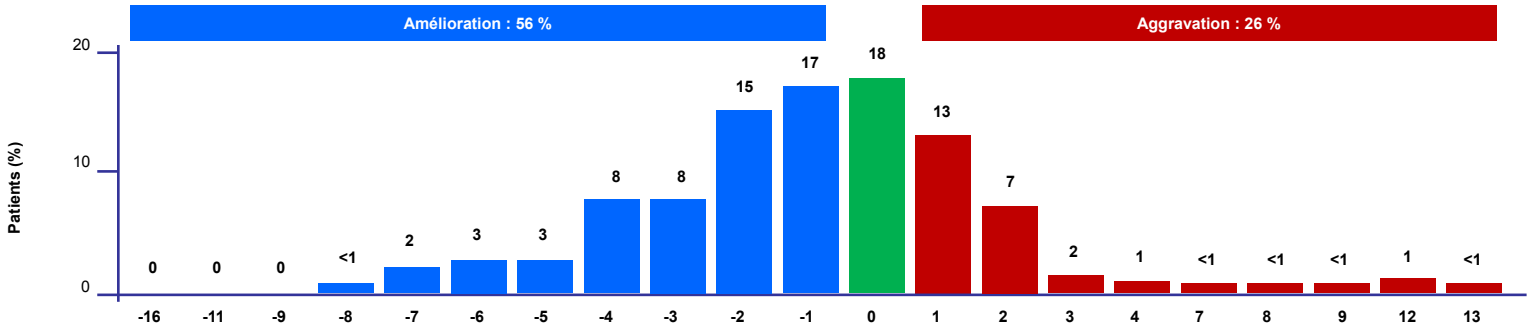


MELD after DAAs: SOLAR-1 et 2 studies

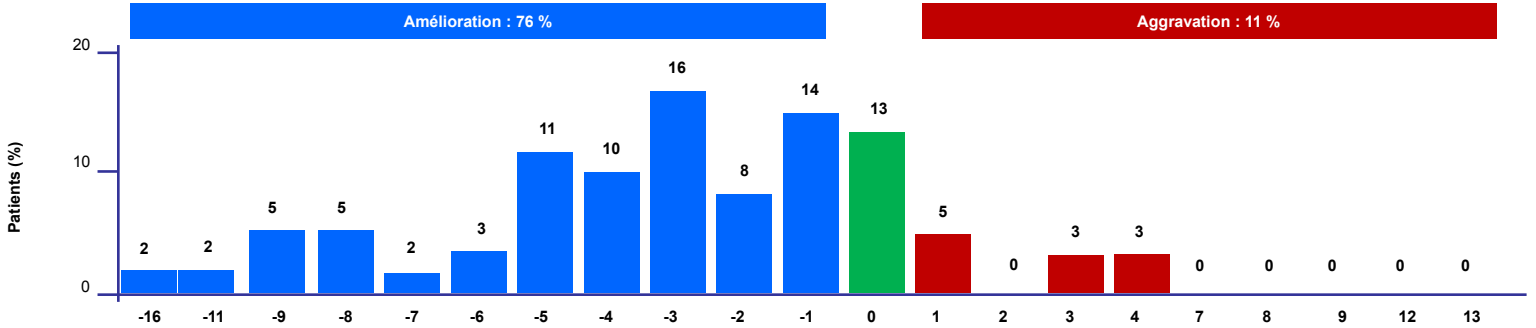
- SOF/LDV + RBV, 12 or 24 weeks, 667 Child B/C patients
- SVR12 : 92 %,

SOLAR-1 et 2

MELD < 15
(n = 199)



MELD ≥ 15
(n = 72)



- Méta-A: 28% of pts display ↓of MELD>3

Welzel, Antivir Ther 2016
Manns Lancet Infect Dis 2016

Delisting ? The European Cohort

- 142 pts
- MELD < 16 (49 %) ; 16-20 (41 %) ; > 20 (10 %)
- Fup: 28 months

34/103 of pts inactivated, mainly MELD<20

26%

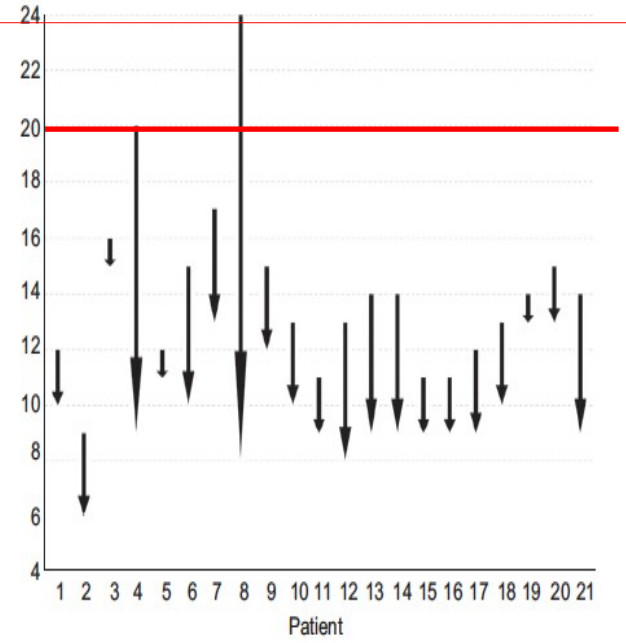


Fig. 4. Delisted patients: individual MELD score at baseline and at delisting.

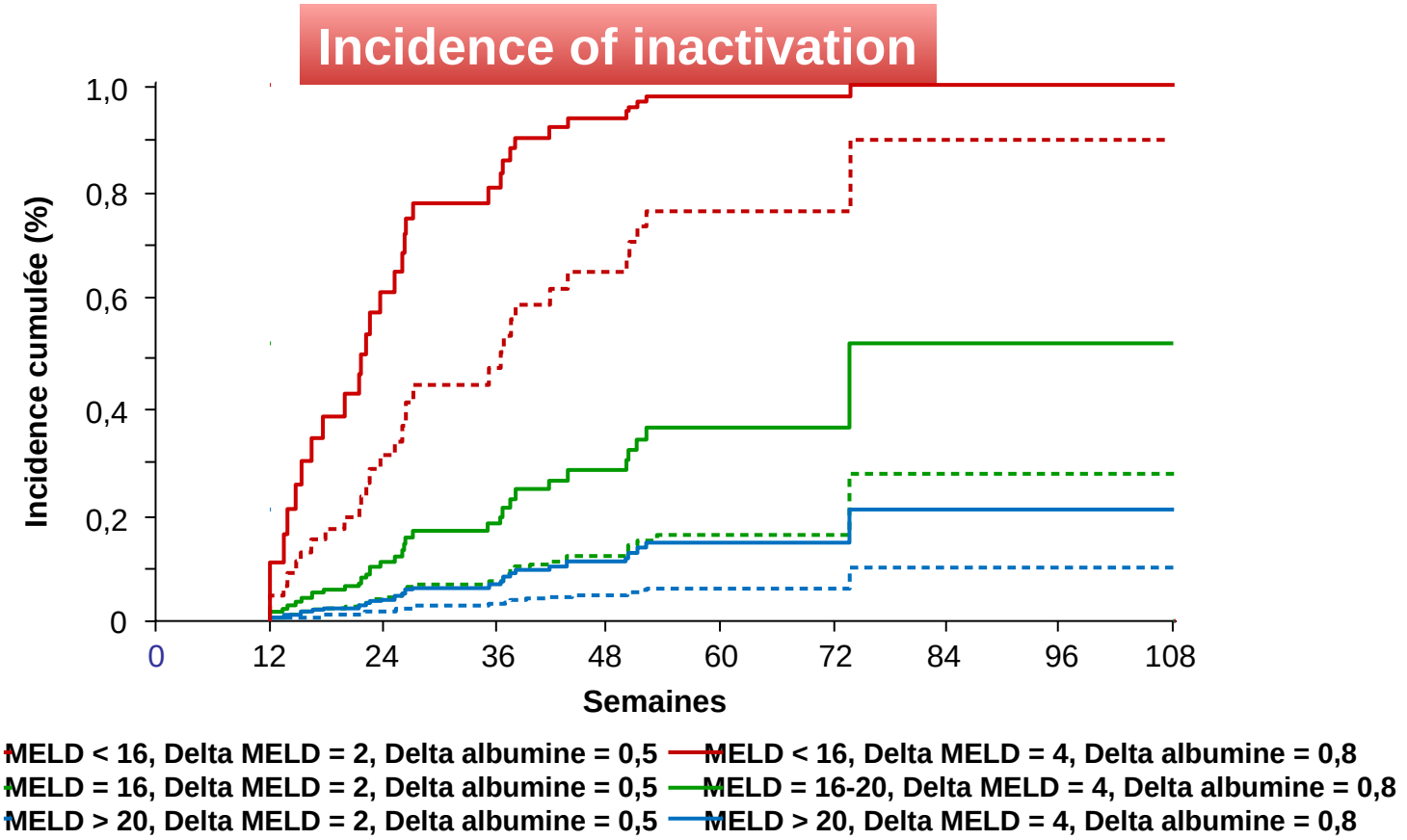
➔ **Delisting if MELD <20**

➔ **After 15 months of Fup after delisting, very low risk of complications**

Belli L et al., J Hepatol 2016
Belli, L et al. EASL. 2017

Delisting ? The European Cohort

- 34/103 patients inactivated, essentially MELD<20



Belli L J Hepatol 2016

How would you manage this patient: personal opinion

- Listing for LT and no HCV Tx because of little efficacy of HCV Tx in decompensated patients
- Listing for LT and no HCV Tx because of contra-indication to DAAs in decompensated patients
- **Listing for LT and no HCV Tx because of low probability to have a MELD<15 after Tx ?**
- Listing for LT and HCV Tx to decrease mortality on waiting-list ?
- HCV Tx before listing because of the risk of graft reinfection

Review

JOURNAL OF HEPATOLOGY

ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients

Coordinators: Luca S. Belli[1,2,*,†], Christophe Duvoux[3,†]
Panel of experts (in alphabetical order): Marina Berenguer[12,‡], Thomas Berg[4,‡], Audrey Coilly[11,‡], Isabelle Colle[9,‡], Stefano Fagiuoli[6,‡], Saye Khoo[7,‡], Georges Philippe Pageaux[8,‡], Massimo Puoti[10,‡], Didier Samuel[11,‡], Mario Strazzabosco[2,5,‡]

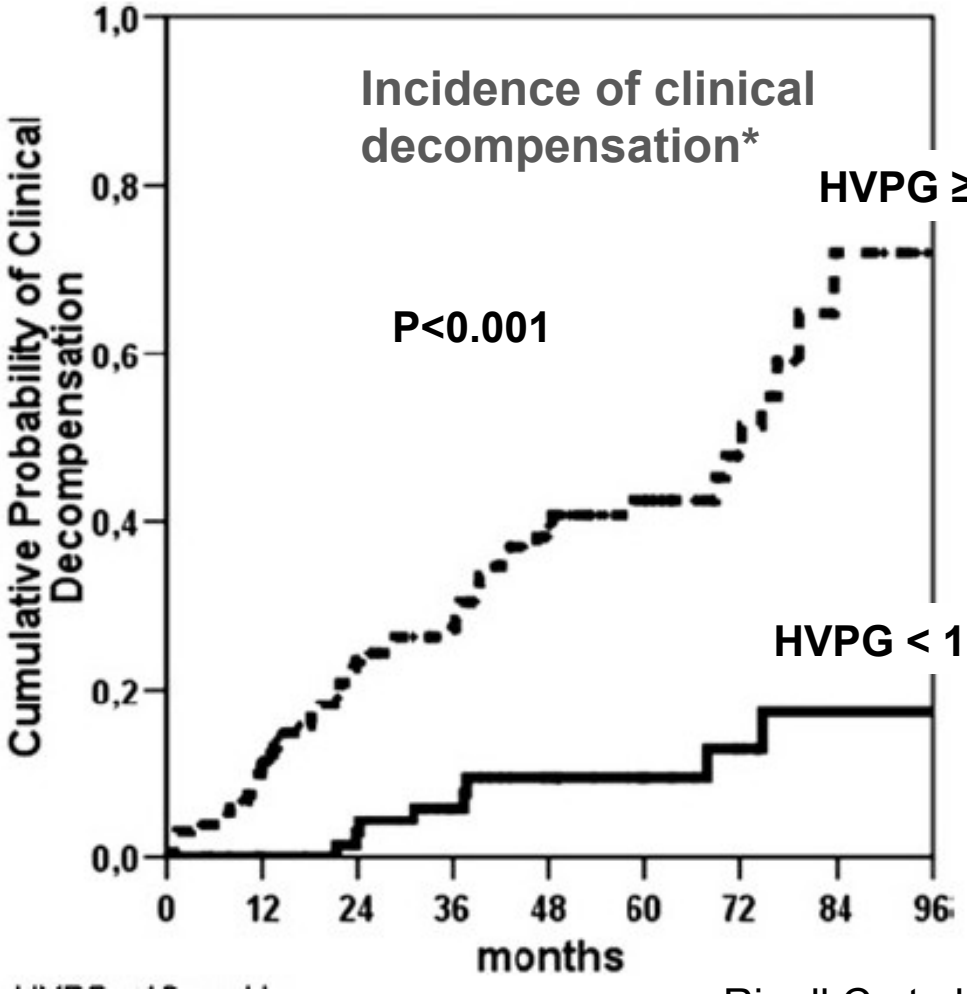
12. In patients with high MELD scores (>20) and expected prolonged waiting time, the risk of a MELD purgatory effect should be balanced against the benefit of reducing the risk of death on the waiting list associated with MELD reduction. GRADE II-3

15. Patients with baseline MELD between 21 and 25 (typically advanced Child-Pugh C):
    - A minority of these patients, specifically those with acute-on-chronic liver failure, may undergo a substantial clinical improvement after DAA treatment which makes inactivation on the waiting list possible. For these patients, a case-by-case multidisciplinary decision is advised. GRADE II-3.

Conclusion

- HCV treatment with DAAs is doable in decompensated cirrhotic pts
- Patients treated before LT must have a high probability of delisting
- In patients awaiting LT with MELD>20, a case by case discussion is mandatory
- HCV treatment with DAAs after LT is highly effective and easy

HVPG is a predictive factor of clinical decompensation



*Variceal Bleeding or EH or Ascites

Ripoll C et al., Gastroenterology 2007

DAAs safety in severe patients

- 3 + 1 cirrhotic pts with comorbidities

[Selected Reports]

CHEST

Severe Pulmonary Arterial Hypertension in Patients Treated for Hepatitis C With Sofosbuvir

Sébastien Renard, MD, MSc; Patrick Borentain, MD, PhD; Erwan Salaun, MD; Sanaa Benhaourech, MD; Baptiste Maille, MD; Albert Darque, MD; Sylvie Bregigeon, MD; Philippe Colson, PharmD, PhD; Delphine Laugier, MD; Martine Reynaud Gaubert, MD, PhD; and Gilbert Habib, MD

- No aggravation of PAHT
- PAHT occurrence in 3 pts F3-F4, improved

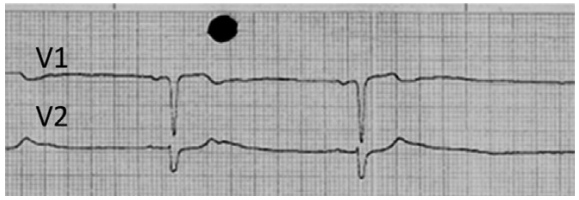
Direct-Acting Antiviral Medications for Hepatitis C Virus Infection and Pulmonary Arterial Hypertension

Laurent Savale MD, PhD[a, b, c], Marie-Camille Chaumais PharmD, PhD[c, d, e], David Montani MD, PhD[a, b, c], Xavier Jaïs MD[a, b, c], Christophe Hezode MD, PhD[h], Teresa-Maria Antonini MD[a, f, g], Audrey Coilly MD[a, f, g], Jean-Charles Duclos-Vallée MD, PhD[a, f, g], Didier Samuel MD, PhD[a, f, g], Gerald Simonneau MD[a, b, c], Marc Humbert MD, PhD[a, b, c], Olivier Sitbon MD, PhD[a, b, c]

DAAs safety in severe patients

- 5 clinical reports

- Amiodaron
- BB ?
- Other ?



Hélène Fontaine, M.D.
Denis Duboc, Ph.D.
Stanislas Pol, Ph.D.
Hôpital Cochin
Paris, France
helene.fontaine@cch.aphp.fr
and Others
for the Cochin Hepatology and Cardiology Group

Gastroenterology 2015;149:1378–1380

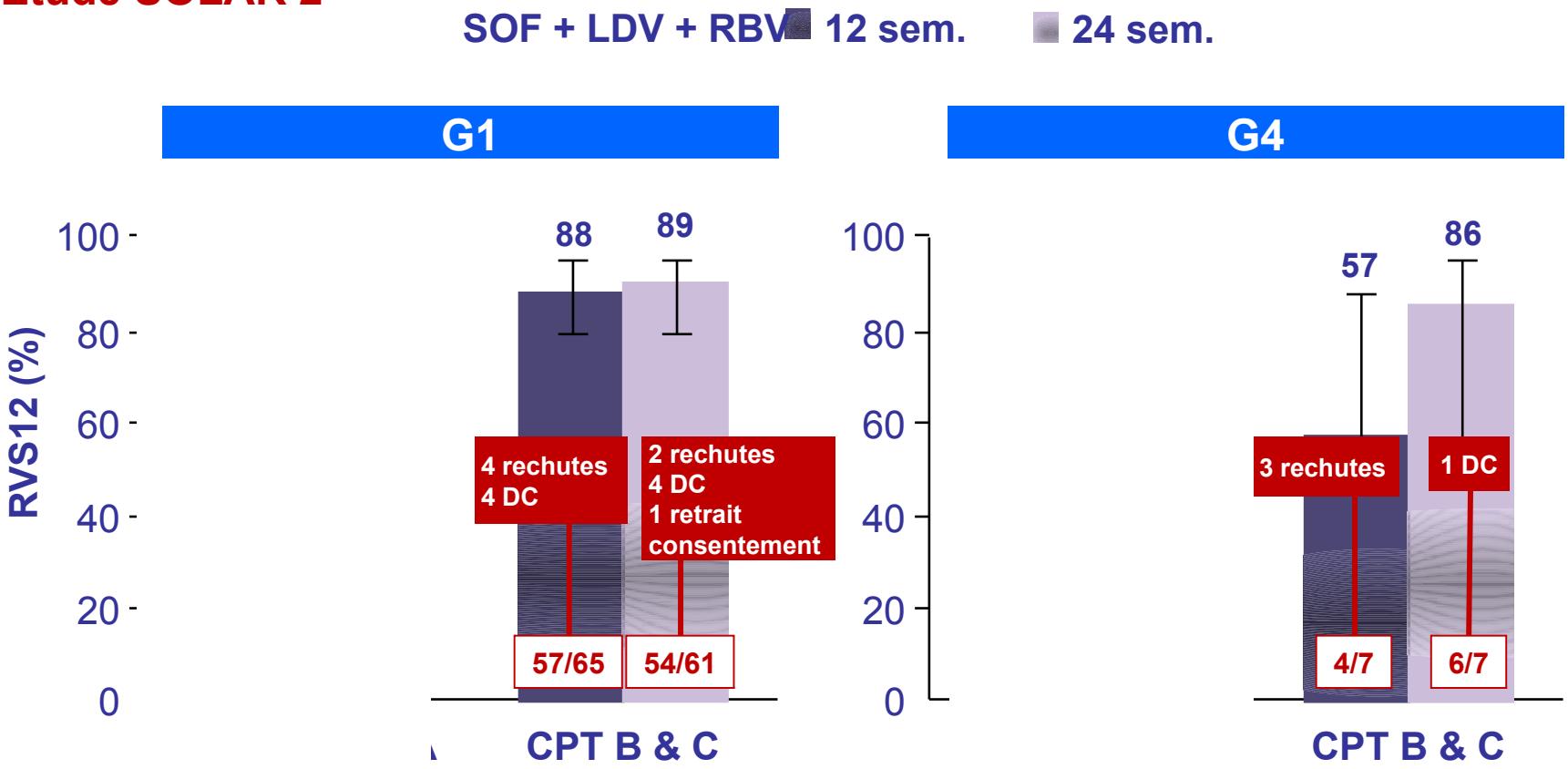
Extreme Bradycardia After First Doses of Sofosbuvir and Daclatasvir in Patients Receiving Amiodarone: 2 Cases Including a Rechallenge

Sophie Renet,[1,*] **Marie-Camille Chaumais**,[1,2,3,*] Teresa Antonini,[3,4,5] Alexandre Zhao,[6] Laure Thomas,[7] Arnaud Savoure,[8] Didier Samuel,[3,4,5] Jean-Charles Duclos-Vallée,[3,4,5] and Vincent Algalarrondo[3,6,9]

- EMA, FDA alerts
- ECG before Sofosbuvir
- Pace Maker if amiodaron

SOF + anti-NS5a before LT

Etude SOLAR 2



- 12 sem, RBV

Manns M, Lancet Infect Dis 2016