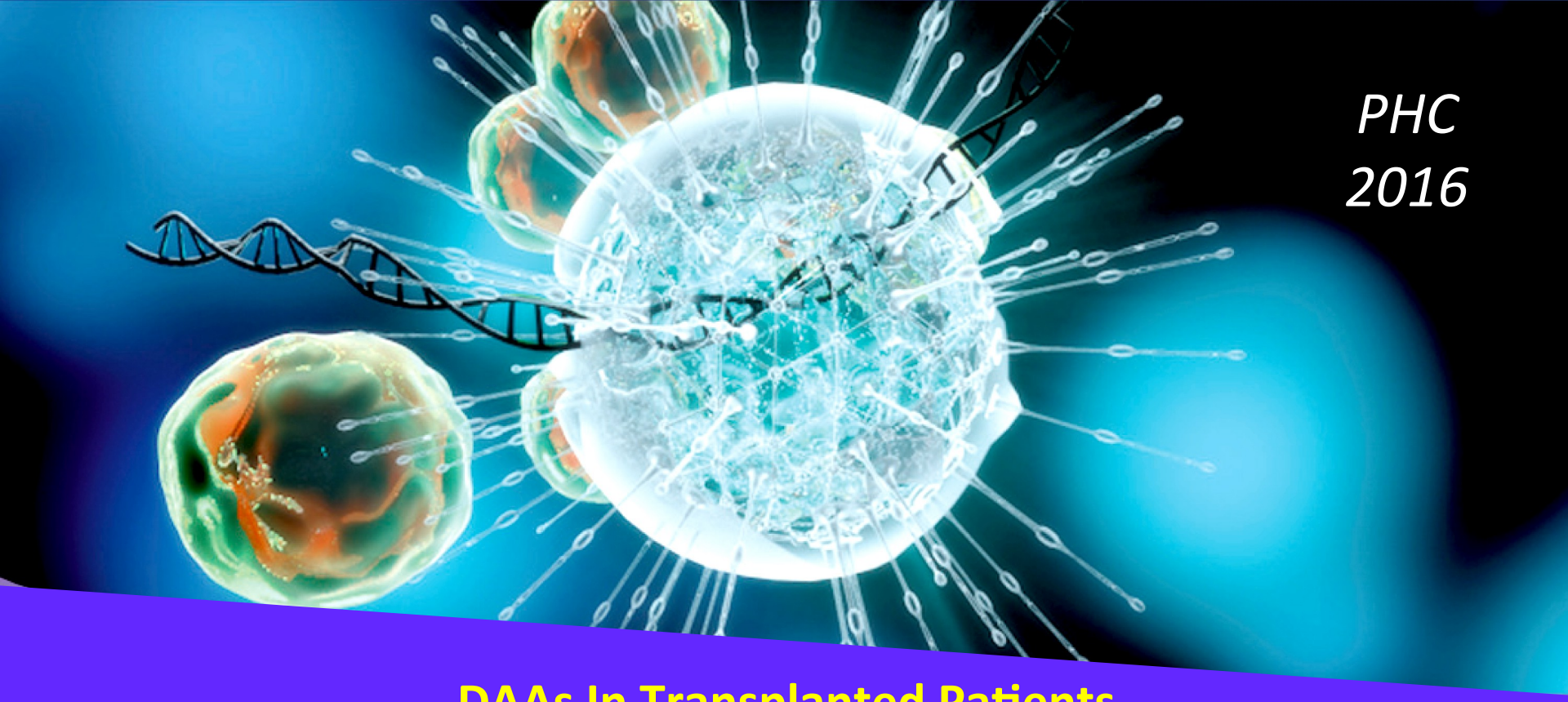

PHC
2016

DAAs In Transplanted Patients

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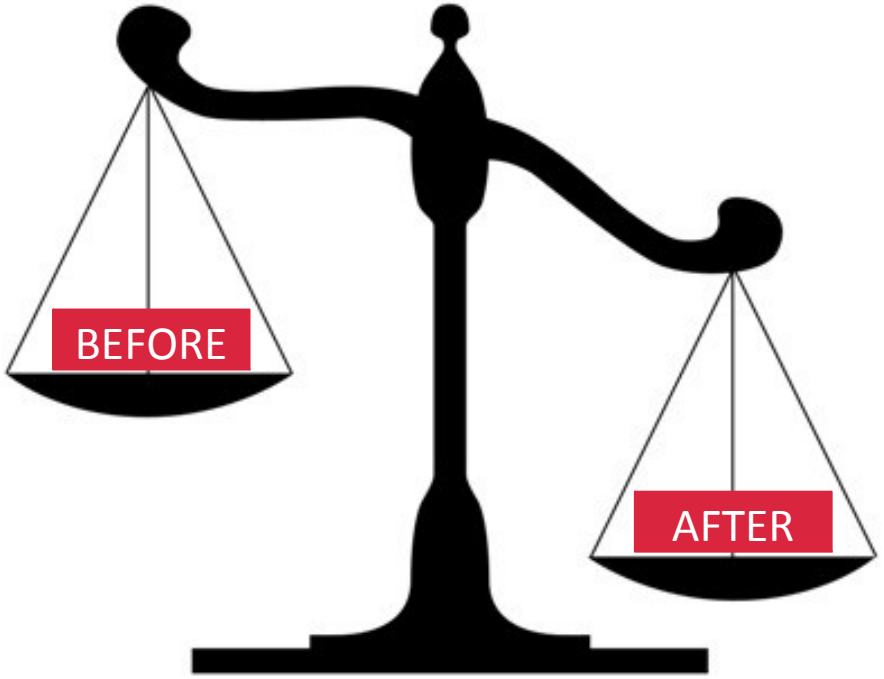
Control HCV Recurrence

- ✓ To achieve HCV clearance is crucial to improve both graft and patient survival

IFN era

- Low efficacy
- Poor safety profile
- Risk of rejection
- Risk of infection



Control HCV Recurrence

- ✓ To achieve HCV clearance is crucial to improve both graft and patient survival

DAA era

- Subtle differences

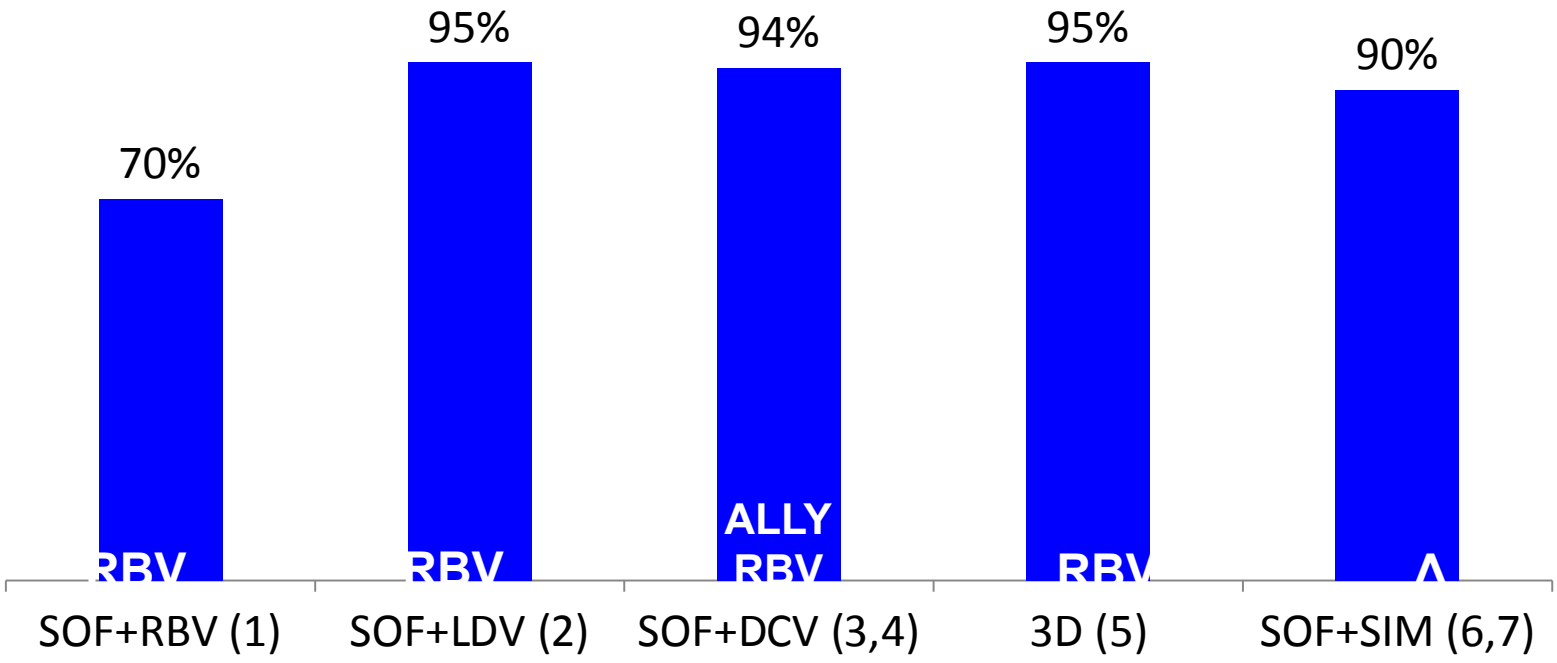
Agenda

- ✓ Difference in efficacy before and after LT?
- ✓ Difference in tolerance?
- ✓ Could we avoid liver transplantation?

Efficacy after LT

Most regimens allow to achieve a SVR12 rate of >90%

Approved regimens



(1) Charlton M, Gastroenterology, 2015; (2) Charlton M, Gastroenterology, 2015; (3) Coilly A, EASL G15, 2015; (4) Poordad F, Etats-Unis, EASL 2015, Abs. L08; (5) Kwo py, NEJM, 2014; (6) Pungpapong S, Hepatology 2015. (7) Reddy R, Etats-Unis, EASL 2015, Abs. O007

Impressive Efficacy in FCH Transplant Patients

Sofosbuvir + Daclatasvir or Sofosbuvir + Ribavirine in 23 Patients with FCH-The Cupilt Cohort

Table 2. Outcome of Clinical Features and Laboratory Tests During and After Treatment

	Week 0	Week 12	Week 24	Week 36	*P*
BMI, kg/m^2	20.5 (18.3–22.7)	22.7 (21.0–24.6)	22.6 (20.9–24.0)	23.7 (21.9–24.7)	<.001
Ascites, n (%)					<.04
Mild/moderate	6 (26)	2 (9)	2 (10)	1 (5)	
Refractory	2 (9)	2 (9)	0 (0)	0	
Bilirubin level, *μmol/L*	122.0 (43.0–191.0)	15.0 (10.0–24.0)	15.0 (12.0–19.0)	11.8 (9.0–20.0) [1]	<.001
Albumin level, *g/dL*	32.3 (25.2–37.8) [3]	36.9 (31.0–42.0) [4]	37.2 (35.8–46.4) [4]	39.2 (37.9–45.0) [6]	<.001
INR	1.1 (1.0–1.2) [3]	1.1 (1.1–1.2) [2]	1.1 (1.0–1.1)	1.0 (1.0–1.1) [7]	.023
Creatinine level, *μmol/L*	91.0 (61.0–108.0)	88.0 (78.0–118.0)	105.0 (86.0–125.0)	101.0 (84.1–118.0)	.017
Platelets, *g/L*	121.0 (79.0–203.0)	135.0 (94.0–177.0)	137.0 (104.0–159.0)	134.0 (103.0–154.0)	.458

Leroy et al, Clin Gastroenterol Hepatol 2015

Impressive Efficacy in FCH Transplant Patients

Sofosbuvir + Daclatasvir or Sofosbuvir + Ribavirine in 23 Patients with FCH-The Cupilt Cohort

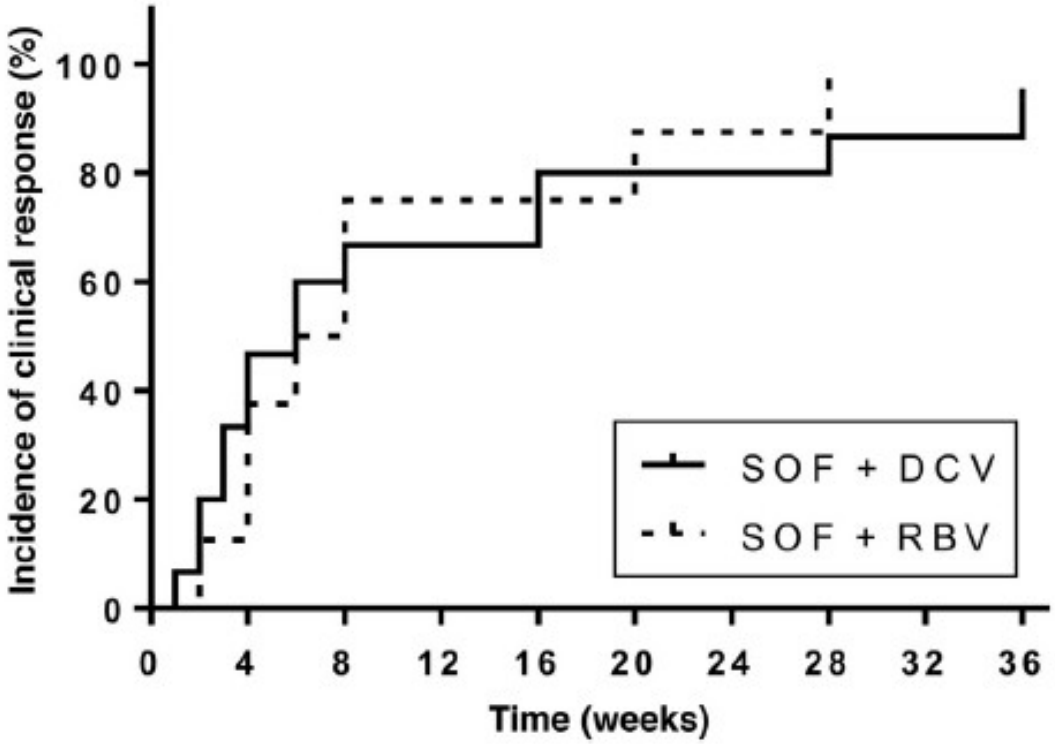
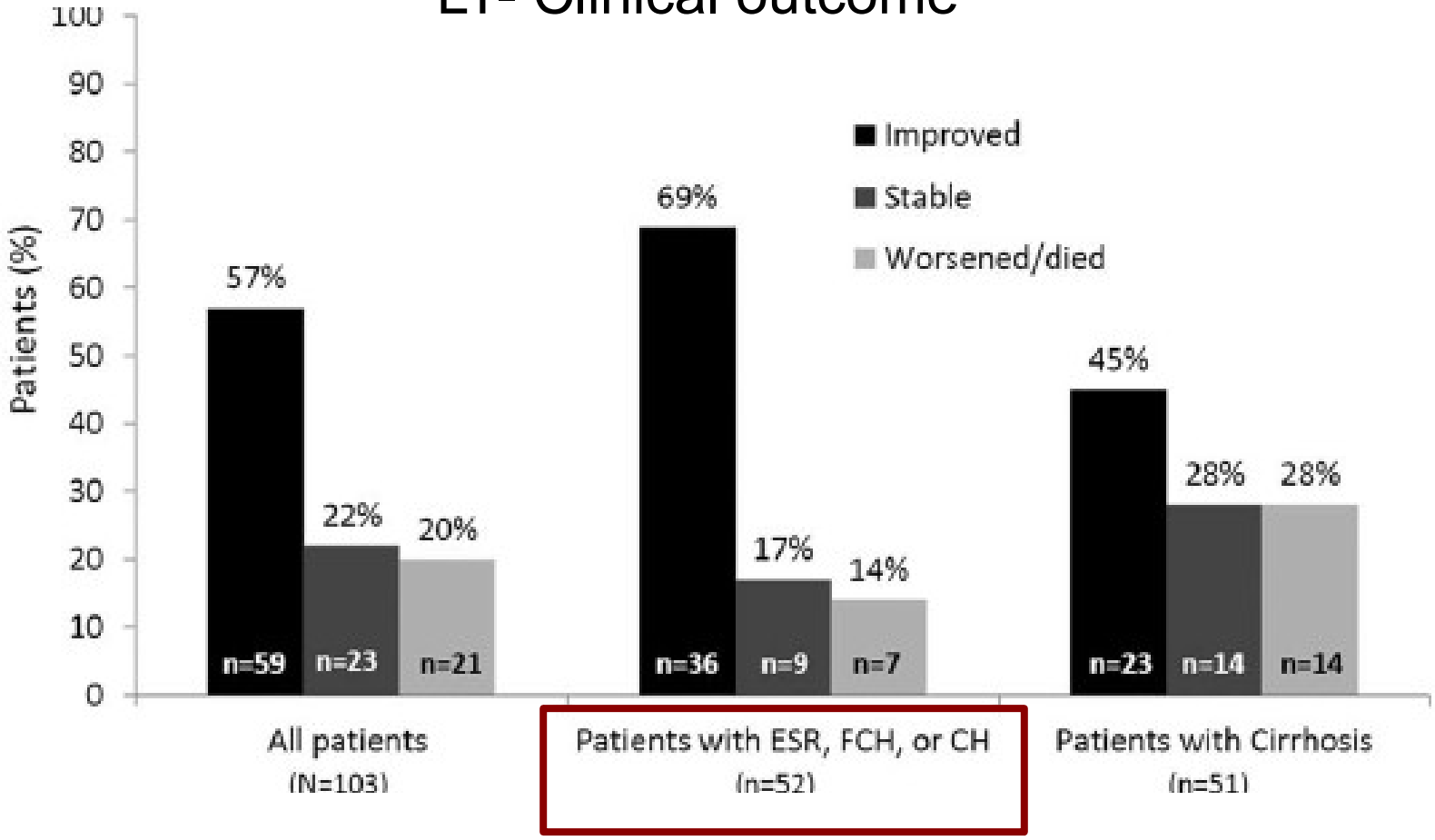


Figure 1. Cumulative incidence of complete clinical response

Leroy et al, Clin Gastroenterol Hepatol 2015

Efficacy Lower in Transplant Patients with Advanced Cirrhosis

Compassionate use of Sofosbuvir + Ribavirine +- Peg IFN After LT- Clinical outcome



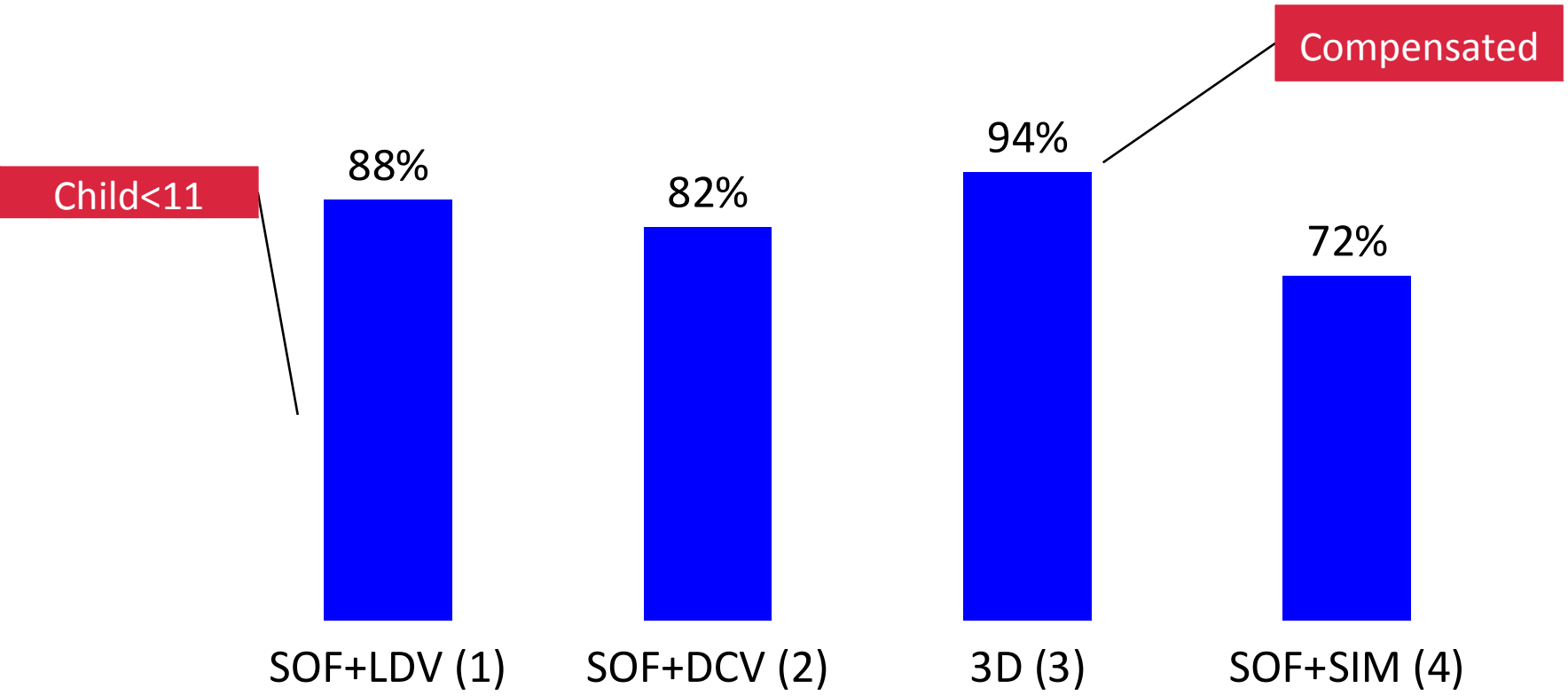
Forns et al, Hepatology 2015

Efficacy before LT

Excellent results in compensated cirrhotic patients

Lower efficacy in decompensated ones

Approved regimens

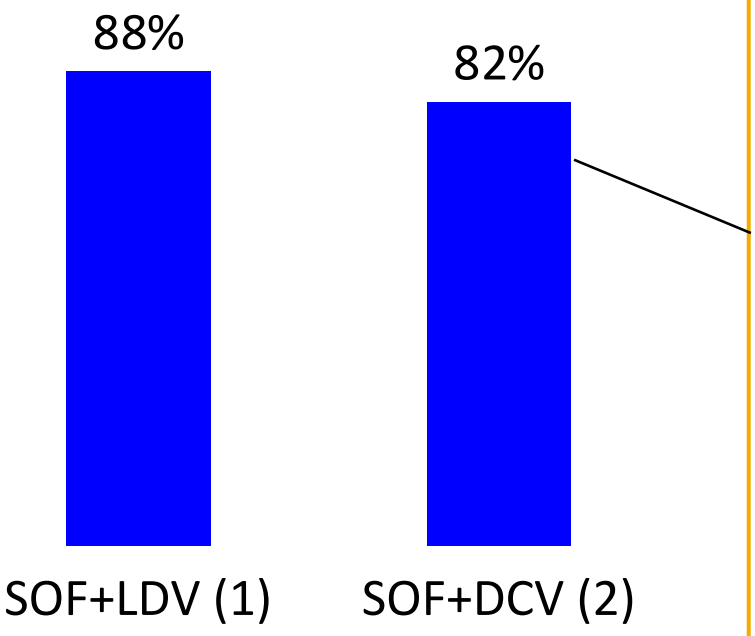


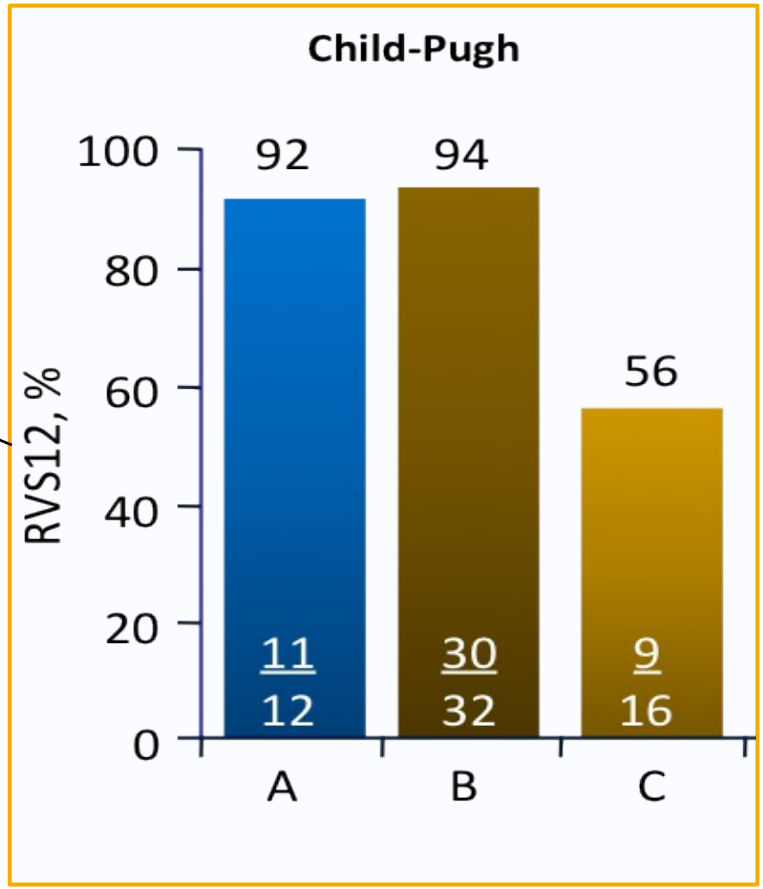
(1) Charlton M. Gastroenterology 2015; (2) Poordad F, Etats-Unis, EASL 2015, Abs. L08; (3) Poordad F, Etats-Unis, EASL 2014, Oral late breaker LB O163 (4) Reddy R, Etats-Unis, EASL 2015, Abs. O007

Efficacy before LT

SVR12 depends on severity of cirrhosis

Using SOF+LDV or 3D, low platelets count and low albumin level are risk factors of relapse



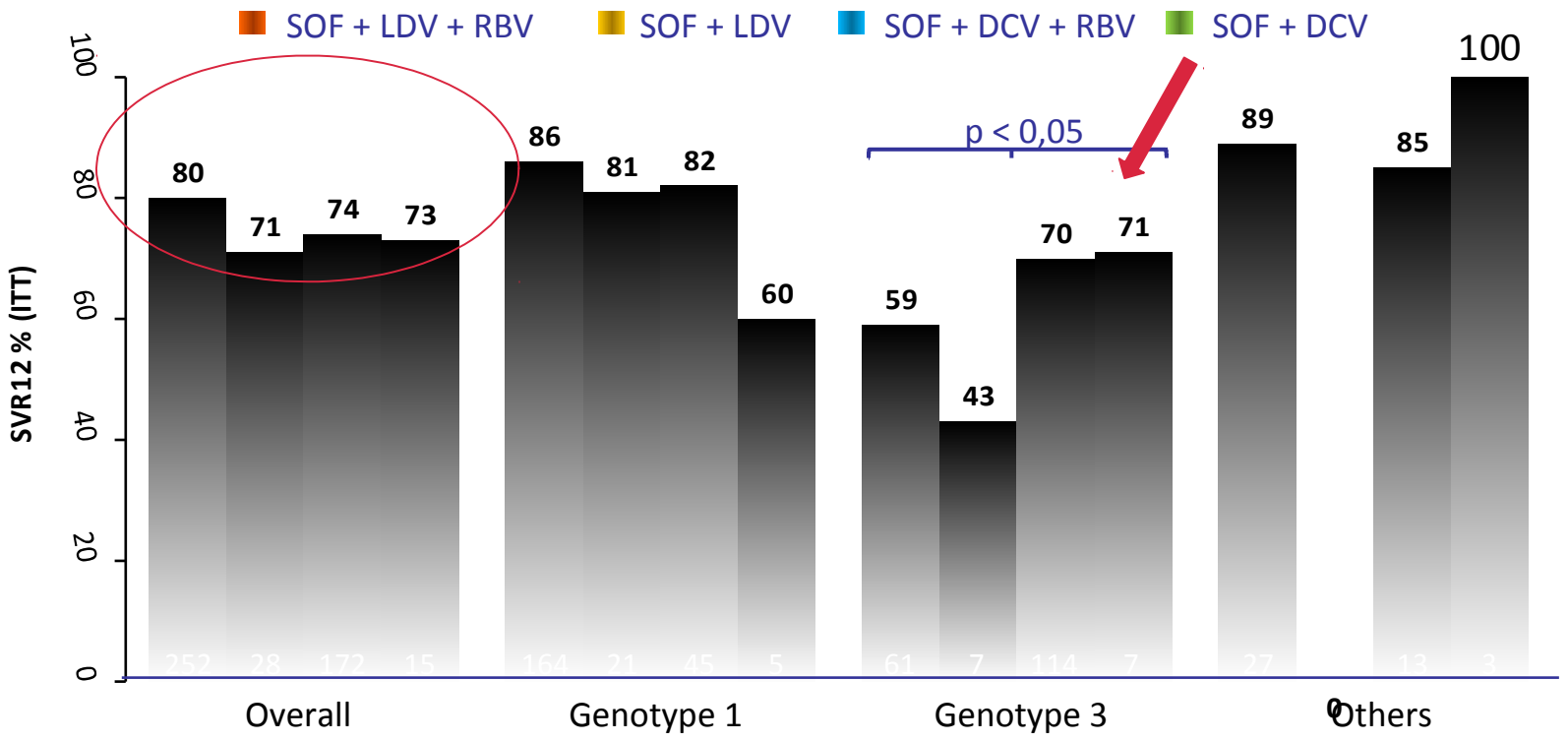


(1) Charlton M. Gastroenterology 2015; (2) Poordad F, Etats-Unis, EASL 2015, Abs. L08; (3) Poordad F, Etats-Unis, EASL 2014, Oral late breaker LB O163 (4) Reddy R, Etats-Unis, EASL 2015, Abs. O007

Efficacy before LT

SVR12 depends also on genotype

Combinaison SOF and NS5A inhibitor ± RBV during 12 weeks
467 cirrhotic patients Child ≥ B7



Foster G, UK, EASL 2015, Abs. O002

Next Generation: Is this going to change?
Astral 4: Sofobuvir + Velpatasvir

Ribavirin still required in most cirrhotic patients

Table 2. Study Outcomes.*

Outcome	Sofosbuvir–Velpatasvir for 12 Wk (N=90)		Sofosbuvir–Velpatasvir plus Ribavirin for 12 Wk (N=87)		Sofosbuvir–Velpatasvir for 24 Wk (N=90)	
	no./total no. (%)	*95% CI*	*no./total no. (%)*	*95% CI*	*no./total no. (%)*	*95% CI*
Sustained virologic response						
All genotypes	75/90 (83)	74–90	82/87 (94)	87–98	77/90 (86)	77–92
Genotype 1a	44/50 (88)	76–96	51/54 (94)	85–99	51/55 (93)	82–98
Genotype 1b	16/18 (89)	65–99	14/14 (100)	77–100	14/16 (88)	62–98
Genotype 2	4/4 (100)	40–100	4/4 (100)	40–100	3/4 (75)	19–99
Genotype 3	7/14 (50)	23–77	11/13 (85)	55–98	6/12 (50)	21–79
Genotype 4	4/4 (100)	40–100	2/2 (100)	16–100	2/2 (100)	16–100
Genotype 6	0	NA	0	NA	1/1 (100)	3–100

Curry NEJM 2016

Conclusion 1: Differences in Efficacy

- ✓ Better results in term of efficacy after LT than before
  - Mainly Child C patients
  - Stage of cirrhosis is still a predictor of efficacy using DAA

- ✓ Unmet medical needs after LT
  - Optimal duration
  - Use of ribavirin
  - Time of treatment initiation

Agenda

- ✓ Difference in efficacy?
- ✓ Difference in tolerance before and after LT?
- ✓ Could we avoid liver transplantation?

Safety after LT

Good safety profile

SAE rate of 20% (mainly due to RBV)

Issue: drug-drug interactions

	Ciclosporine	Tacrolimus
Sofosbuvir		
Sofosbuvir/Ledipasvir	 Ciclosporine AUC - 2%	 Tacrolimus AUC + 13%
Daclastavir		
Simeprevir	 Ciclosporine AUC +4.74	 Tacrolimus AUC +79%
Ombitasvir, paritaprevir, ritonavir, dasabuvir	 Ciclosporine AUC +5.82 Dosage ÷5	 Tacrolimus AUC +57.1 0.5mg/wk ou 0.2mg/2days

Coilly, A. Liver Int. 2015

Safety after LT

Good safety profile

SAE rate of 20% (mainly due to RBV)

Issue: drug-drug interactions

ANRS C023 CUPILT cohort: SOF+DCV

	Tacrolimus	Ciclosporine	Everolimus	MMF
Number of patients	78	37	13	71
Number who changed dosage – n (%)	44 (56 %)	18 (49 %)	5 (38 %)	9 (13 %)

- ✓ Most changes occurred after 4 weeks of treatment, reflecting improvement in liver function more than clinically relevant drug-drug interactions
- ✓ To monitor immunosuppressive drugs is still mandatory

Coilly, A. France, G15, EASL 2015.

Safety before LT

Good safety profile

SAE rate of 20% (mainly due to RBV)

Hepatic function is one issue

Pharmacokinetic changes according to liver function

	Hepatic function impairment			Avoid
	Mild	Moderate	Severe	
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-Mahadevan 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.

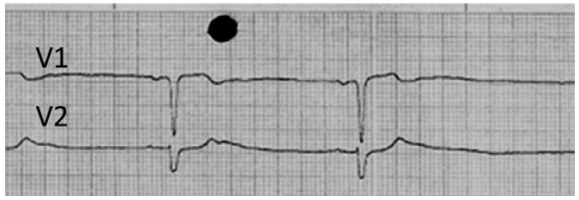
Sofosbuvir and Cardiologic events

5 reported cases

Role of amiodarone

B-Blockers?

Other?



Unexpected adverse events in more severe patients

The NEW ENGLAND JOURNAL of MEDICINE

Bradyarrhythmias Associated with Sofosbuvir Treatment

Hélène Fontaine, M.D.
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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]

Conclusion 2: Differences in Tolerance

- ✓ Safety profiles are excellent before and after liver transplantation.
- ✓ Issues are
  - Drug-drug interactions, mainly with immunosuppressive drugs
  - Anemia Post Transplant (RBV)
  - Hepatic impairment
- ✓ Both issues argue for the use of NS5A inhibitors more than protease inhibitors

Agenda

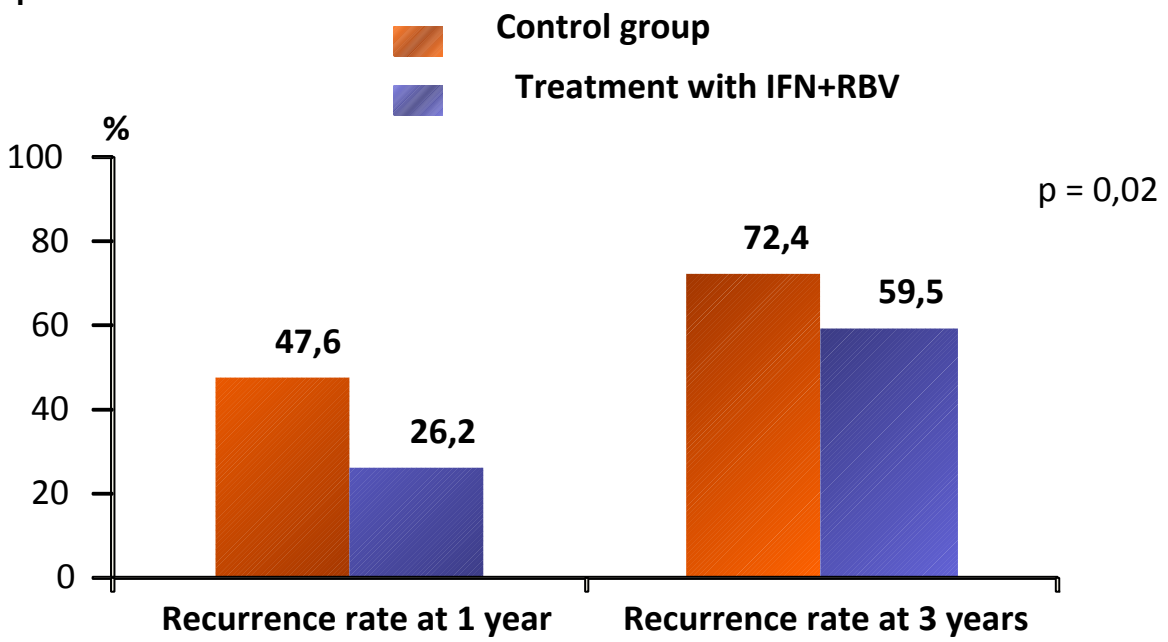
- ✓ Difference in efficacy?
- ✓ Difference in tolerance?
- ✓ Could we avoid liver transplantation?

HCC patients

No withdrawal of list

Improvement in hepatic function could make a treatment feasible to control HCC on waiting list

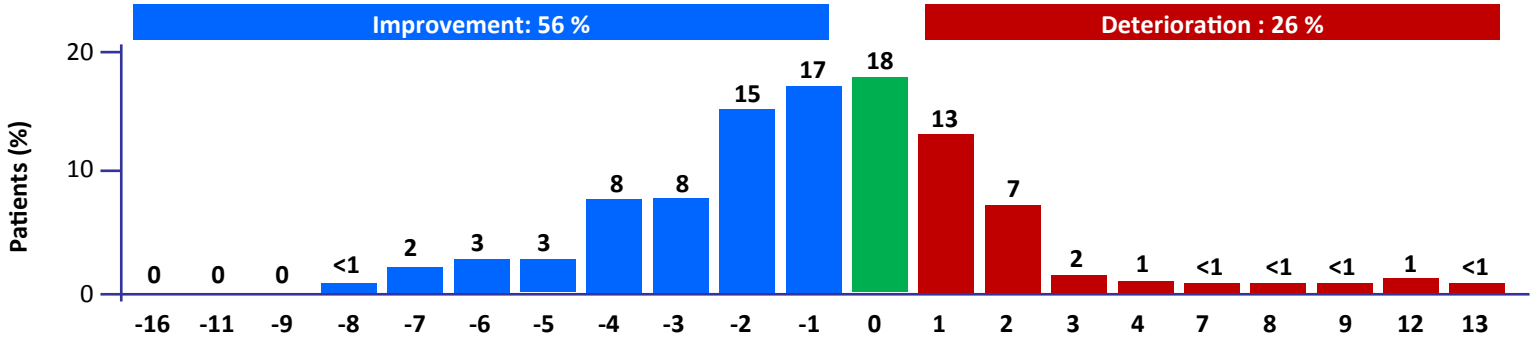
N=84
RF



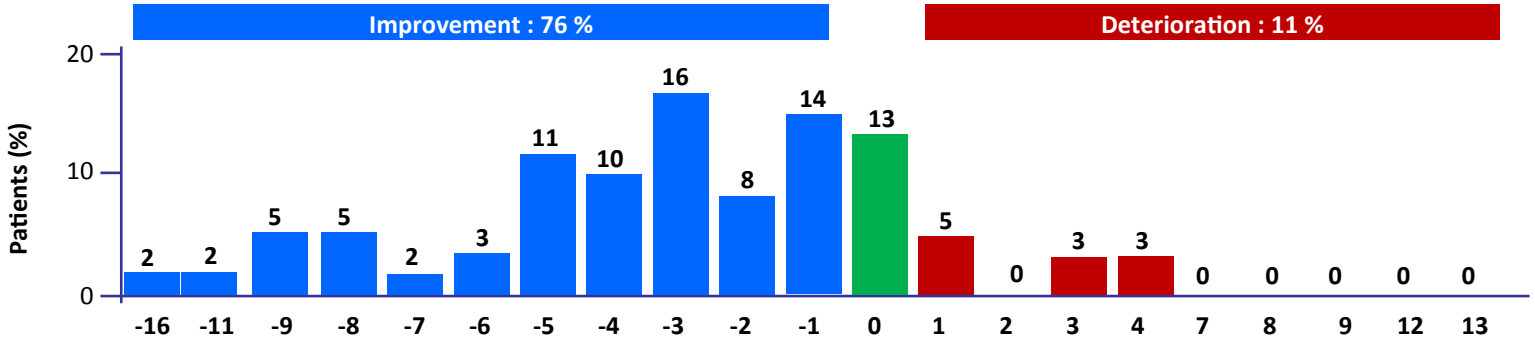
Zhang N, China, EASL 2014, Abs. P994

Variations of MELD score Baseline/EOT in SOLAR I and II studies among Child>B cirrhotics

Baseline MELD < 15 (n = 199)



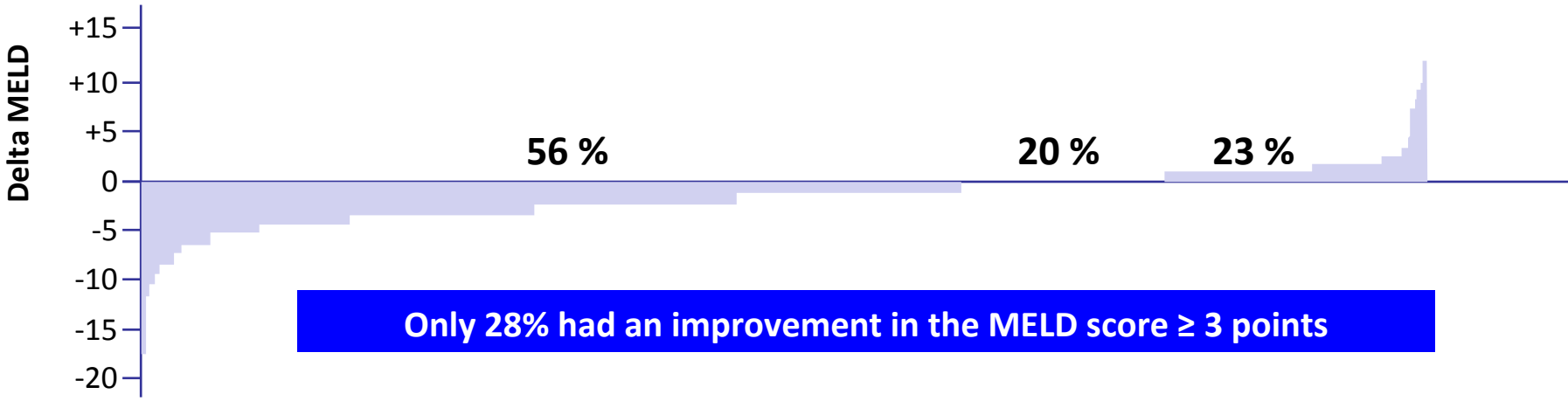
Baseline MELD ≥ 15 (n = 72)

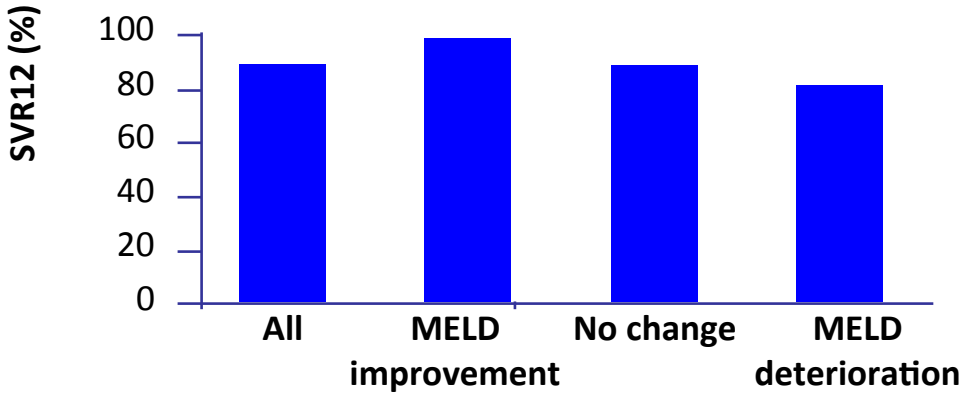


Gane EJ, New Zealand, AASLD 2015, Abs. 1049

Association Between Improvement and SVR

Meta-analyses of 5 studies





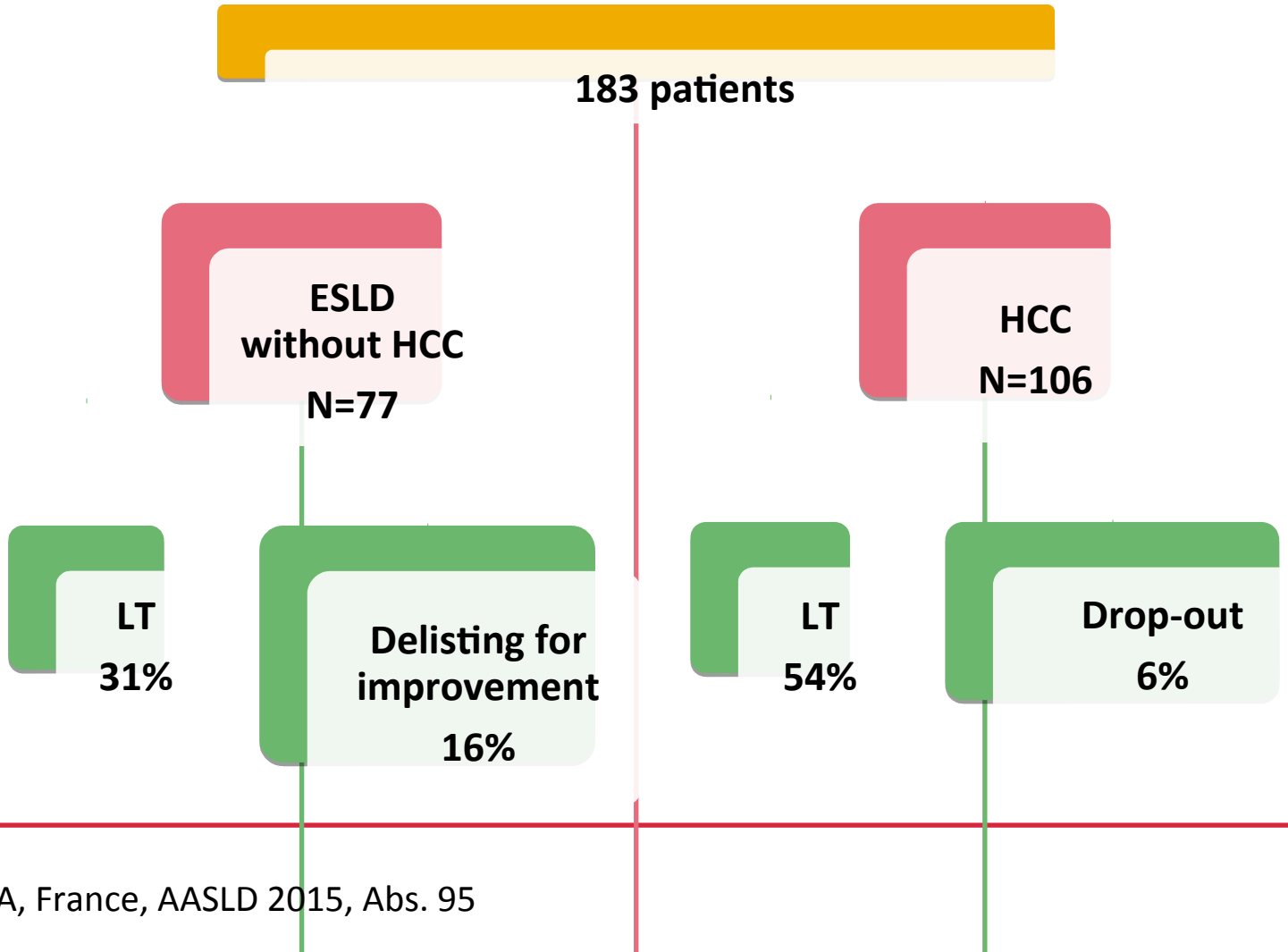
- ✓ Some patients improve without achieving SVR
- ✓ Although achieving SVR, some patients worsen (comorbidities?)

Munoz J, USA, AASLD 2015, Abs. 202

Is there a Point of no Return?

National cohort study in patients waiting for LT in France

SVR12 = 88 %

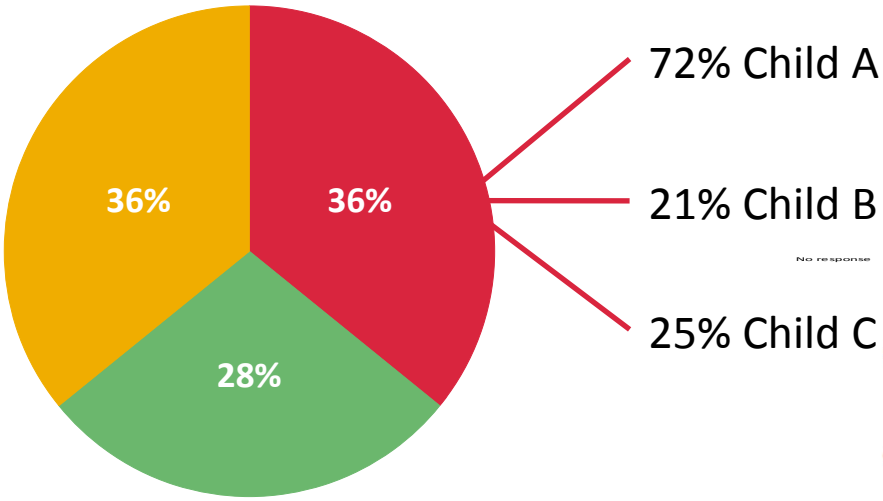


Coilly A, France, AASLD 2015, Abs. 95

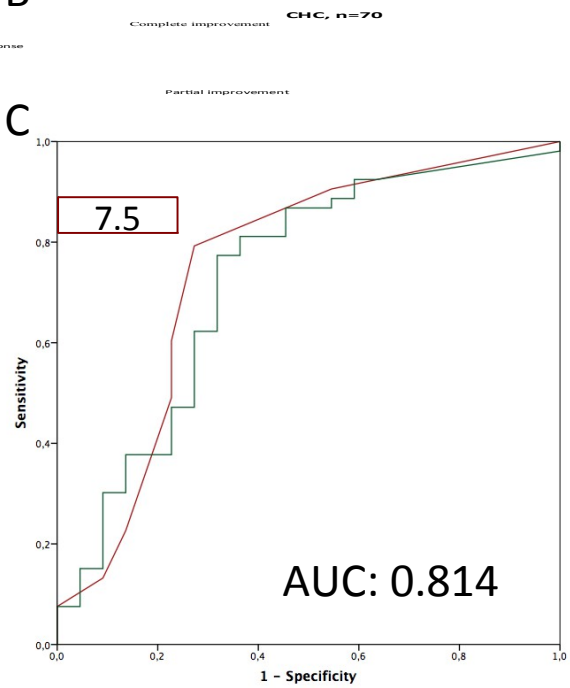
Is there a Point of no return?

National cohort study in patients waiting for LT in France: **SVR12 = 88 %**

Cirrhosis, n=53



MELD score could not be the good marker



Child-Pugh score

MELD score

Coilly A, France, AASLD 2015, Abs. 95

Taking into account the System of Organs Allocation

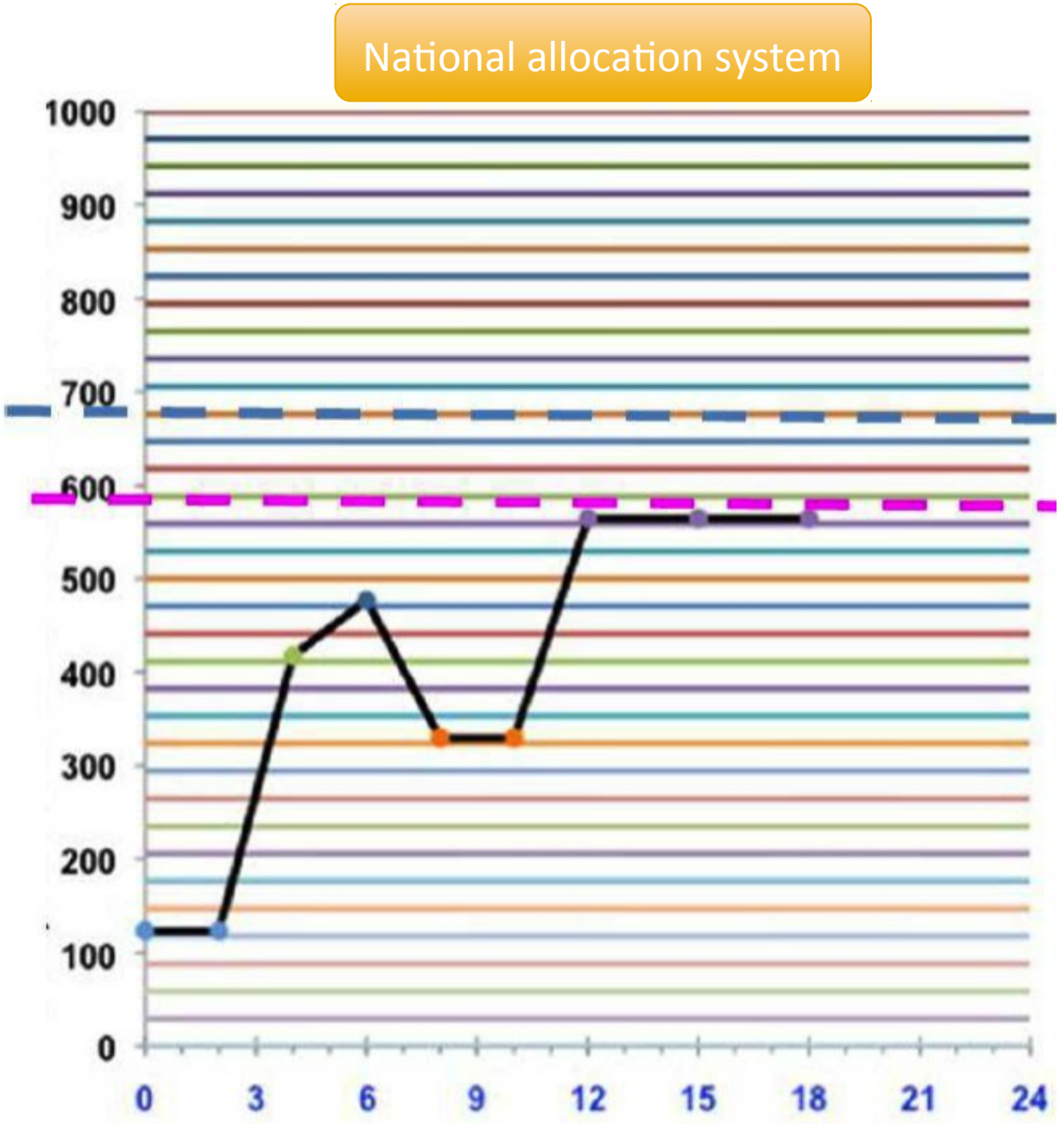
Deaceased donor

Male 61 yo, G1b

ESLD without HCC

MELD 23 after SBP

Listed for LT



Taking into account the system of organs allocation

Deaceased donor

Male 61 yo, G1b

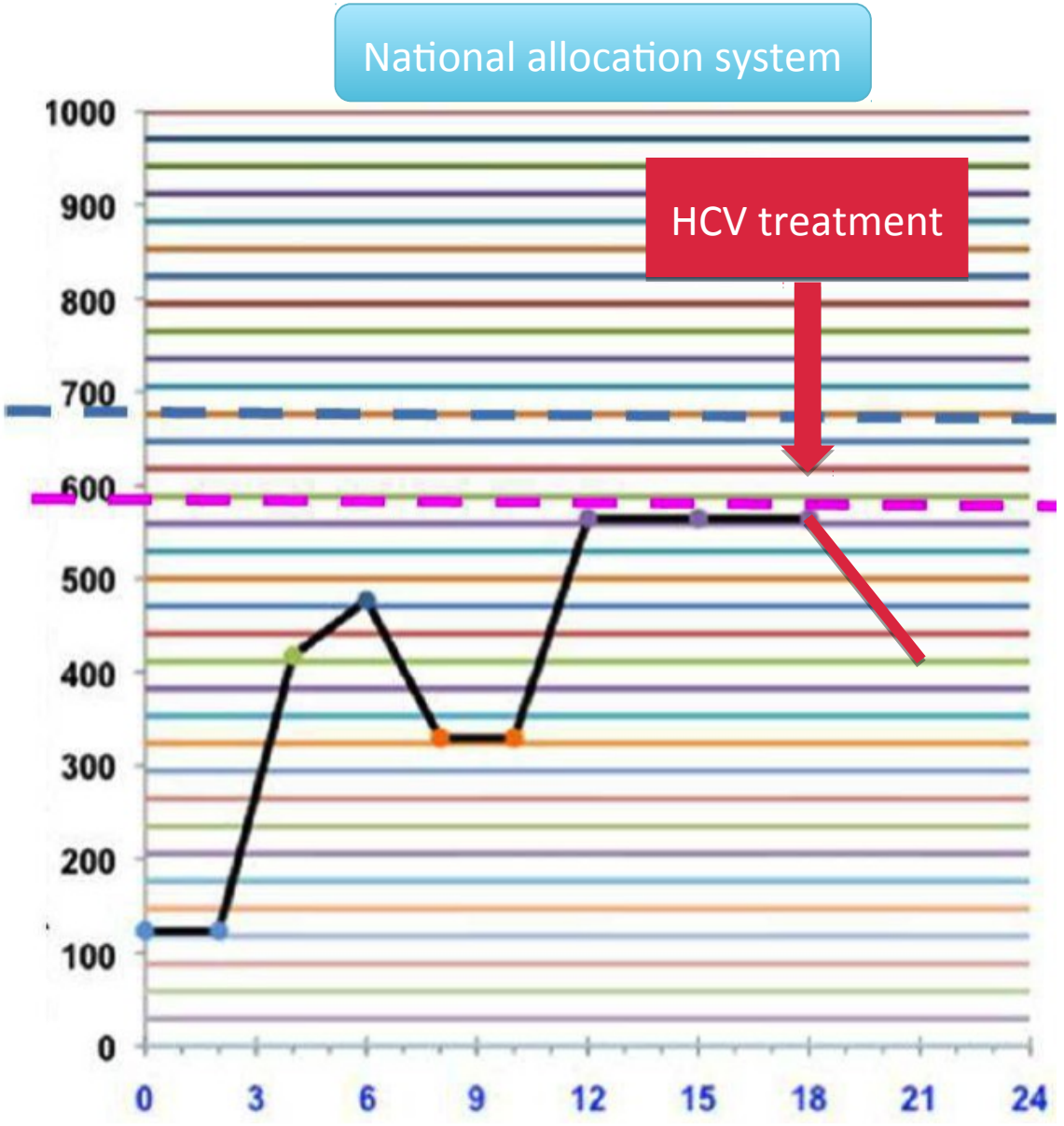
ESLD without HCC

MELD 23 after SBP

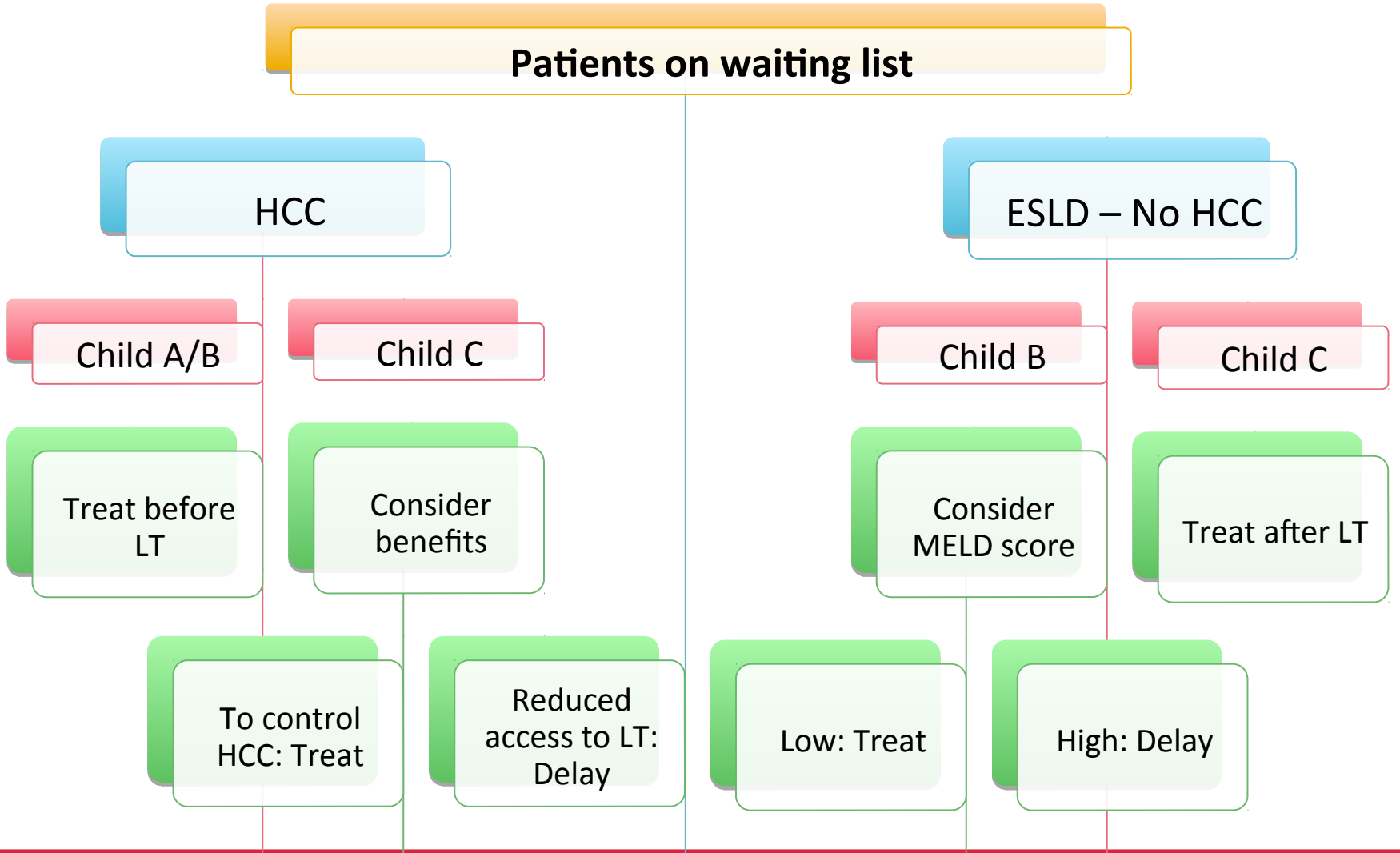
Listed for LT

- Ascites
- Covert HE

LT still indicates but no more access…



Conclusion 3: Management Proposal
Treatment with DAA Before or After LT



Take Home Messages

Treat hepatitis C using DAA before or after LT? Both strategies are feasible with excellent efficacy results and good safety profiles

Regarding efficacy, better results are achieved after LT than before in decompensated cirrhotic patients

Regarding safety, drug-drug interactions and degree of hepatic impairment are still issues, and favor the use of NS5A inhibitors

Withdraw patients of waiting list is feasible and should concern about 30% of patients.

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And all the Team at The CHB