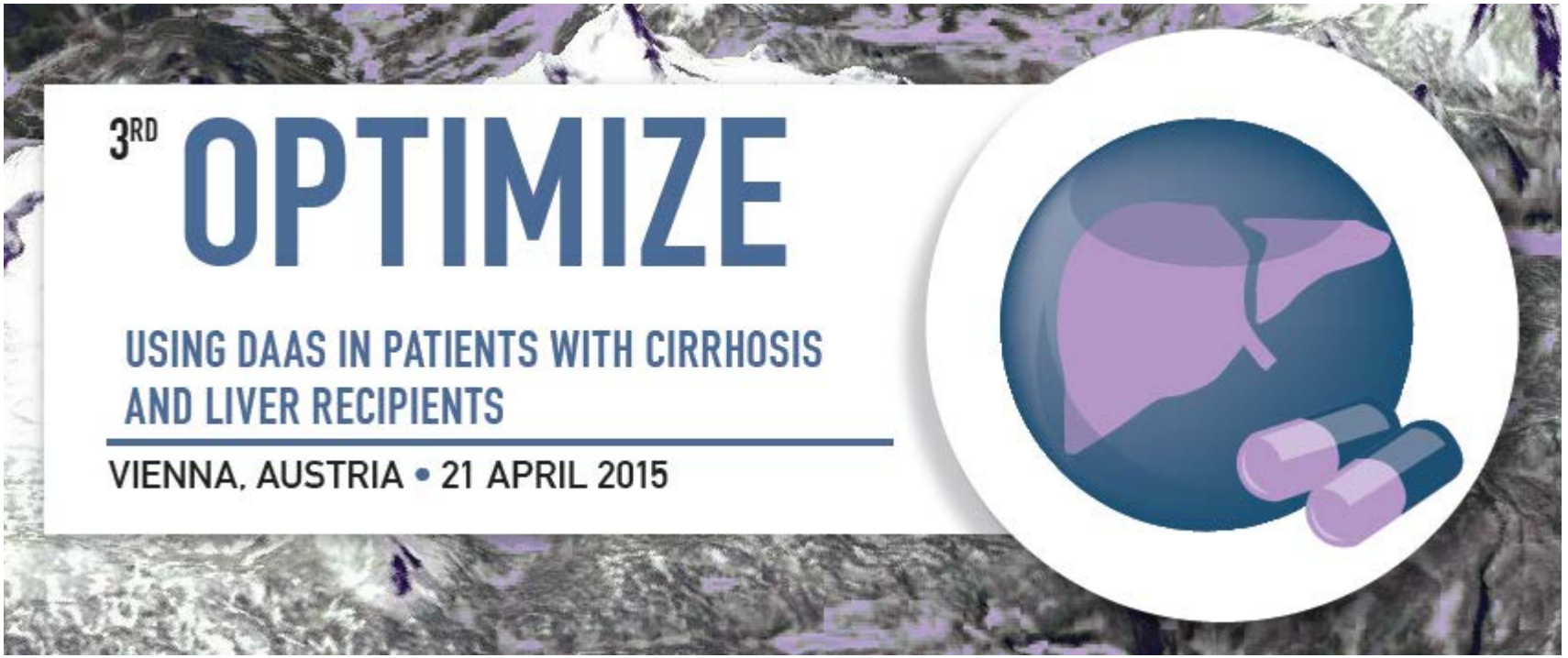

Treatment of Hepatitis C Recurrence after Liver Transplantation

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Hospital Clínic Barcelona

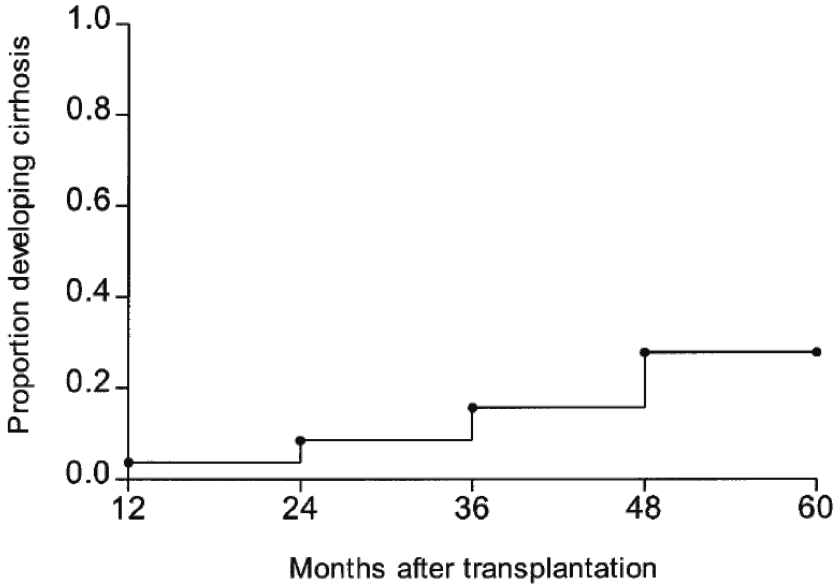
Agenda

1. Introduction

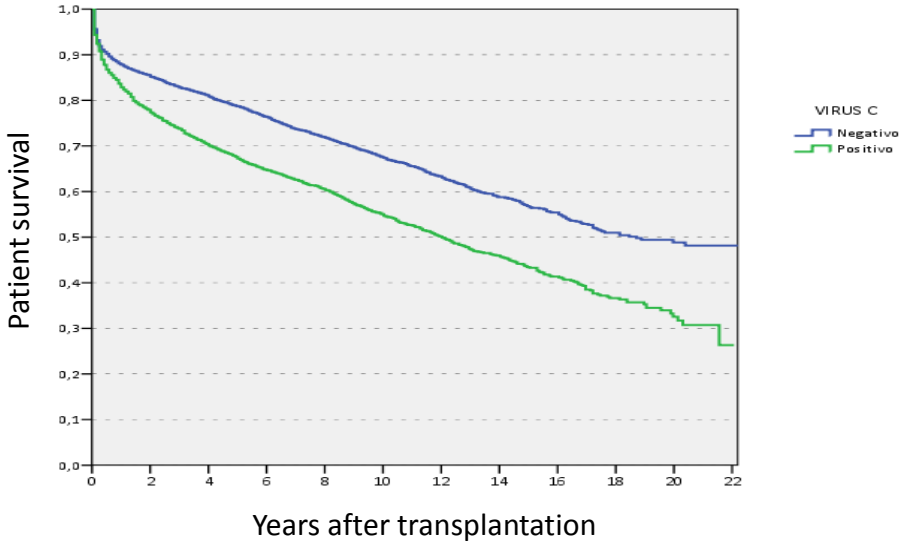
2. Treatment options for hepatitis C recurrence after transplantation
   - Clinical trials
   - Real life cohorts

3. Unsolved issues

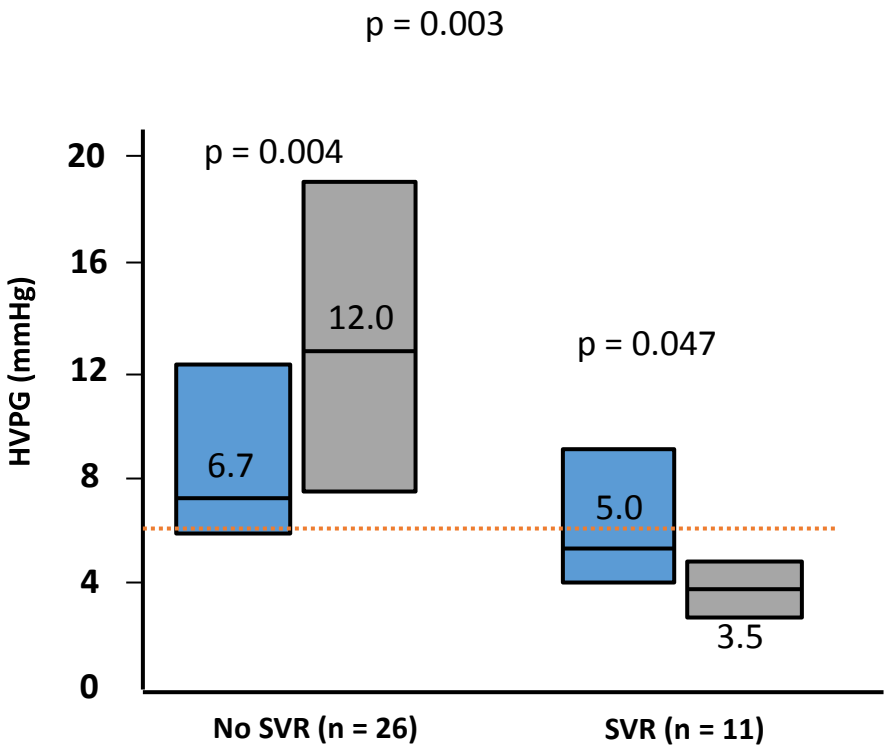
Hepatitis C and Liver Transplantation



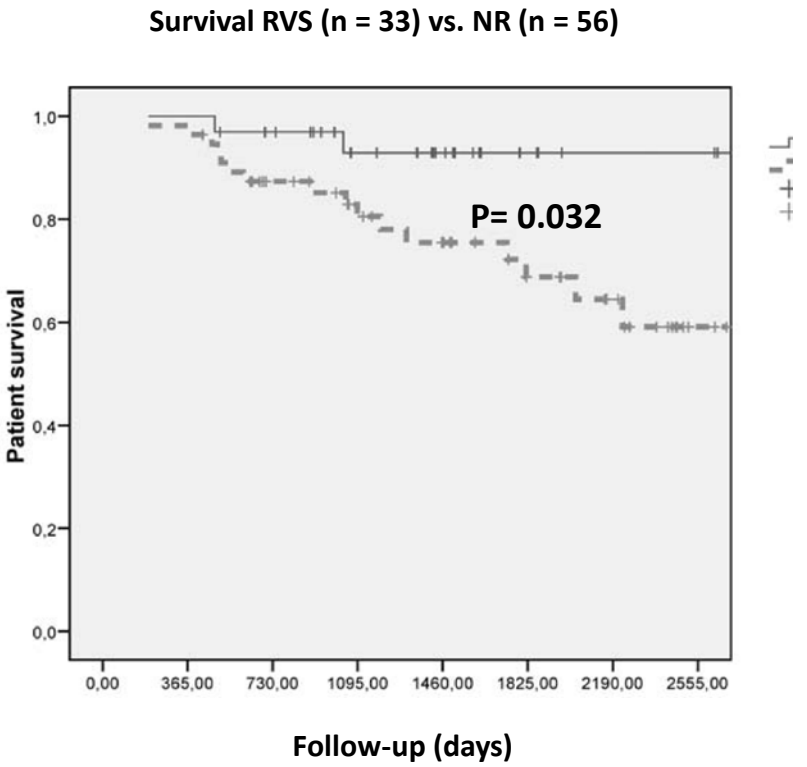
Prieto et al, Hepatology 1999



Hepatitis C and Liver Transplantation



Carrion JA, et al. Gastroenterology 2007



Berenguer M et al, Am J Transpl 2008

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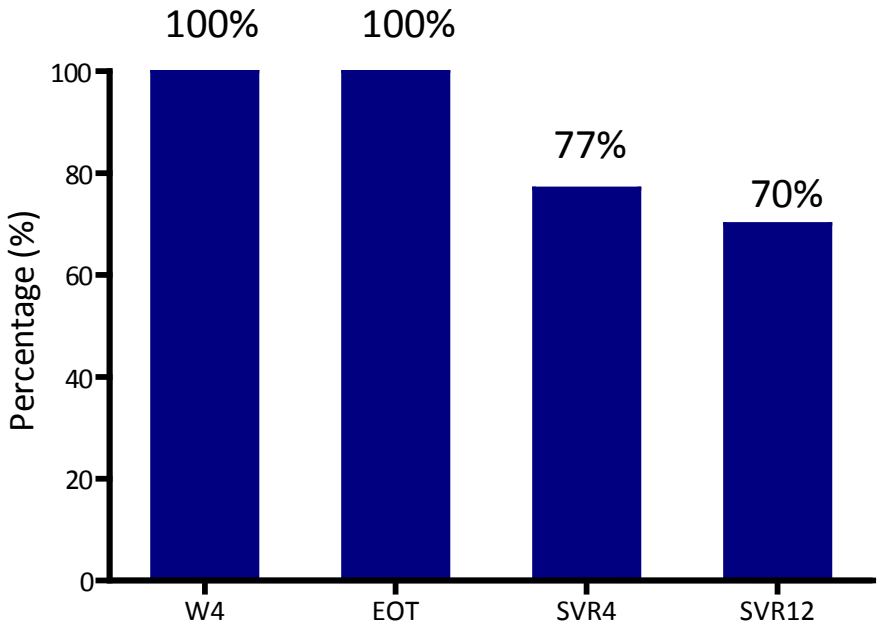
Sofosbuvir + RBV

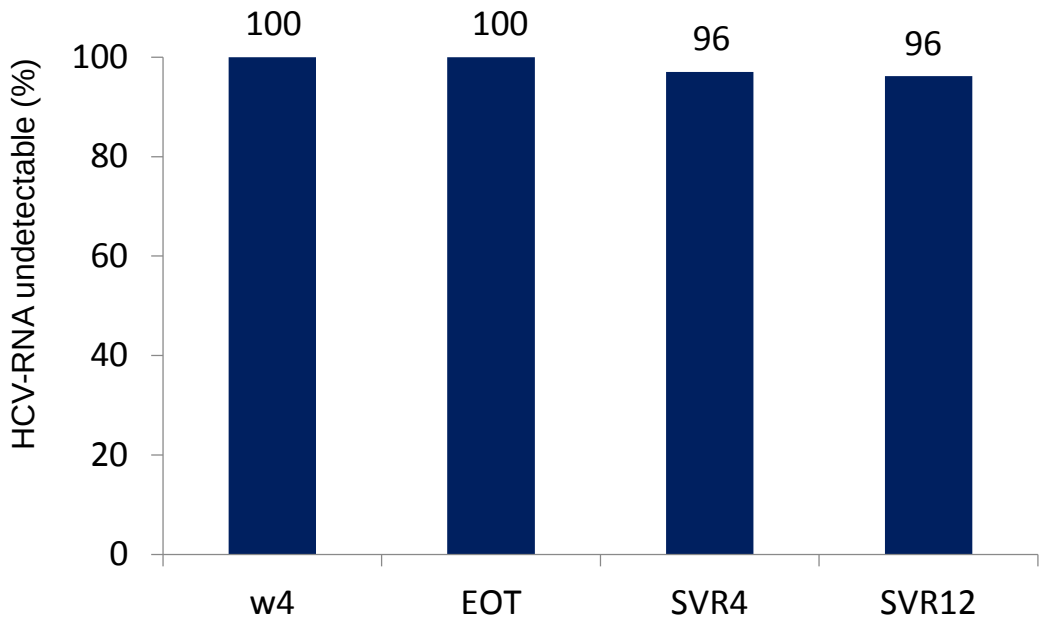
- 40 LT recipients (>6mo)
- 33 were G1
- 16 cirrhotics
- DC due to AE =2
- Relapse 9 patients



Charlton et al, Gastroenterology 2015

Ombitasvir/Paritaprevir/r + Dasabuvir + RBV

- Mild-Moderate fibrosis (F0-F2)→ n=34
- G1a → 85%

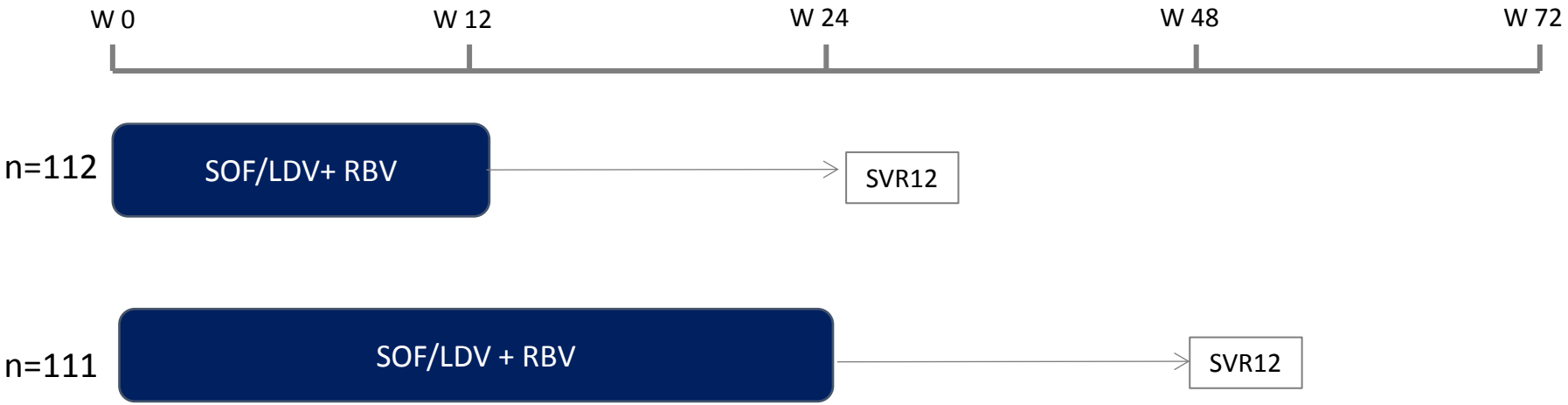


Anemia	**17%**
Rejection	0
Renal Impairement	0
Early Discontinuation	**3%**
SAEs	**6%**
Deaths	0

- CNI adjustment (Tac 0.5mg/w and CyA 1/5 of previous dose)

Kwo P, NEJM 2014

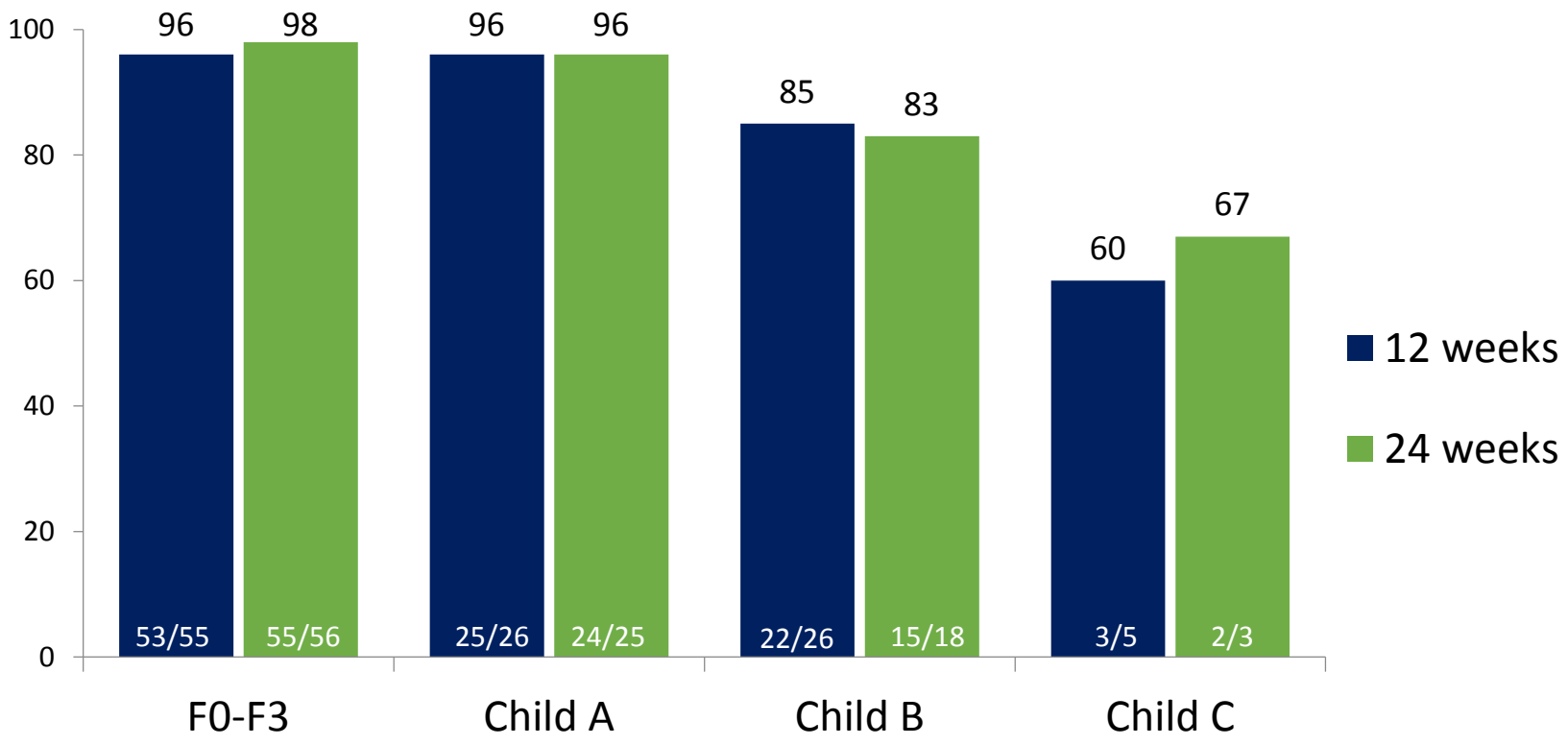
Ledipasvir/Sofosbuvir + RBV



Randomized trial (1:1), Genotype 1 or 4, naïve or treatment experienced
F0-F3, Child A, B, C

Reddy et al, AASLD 2014

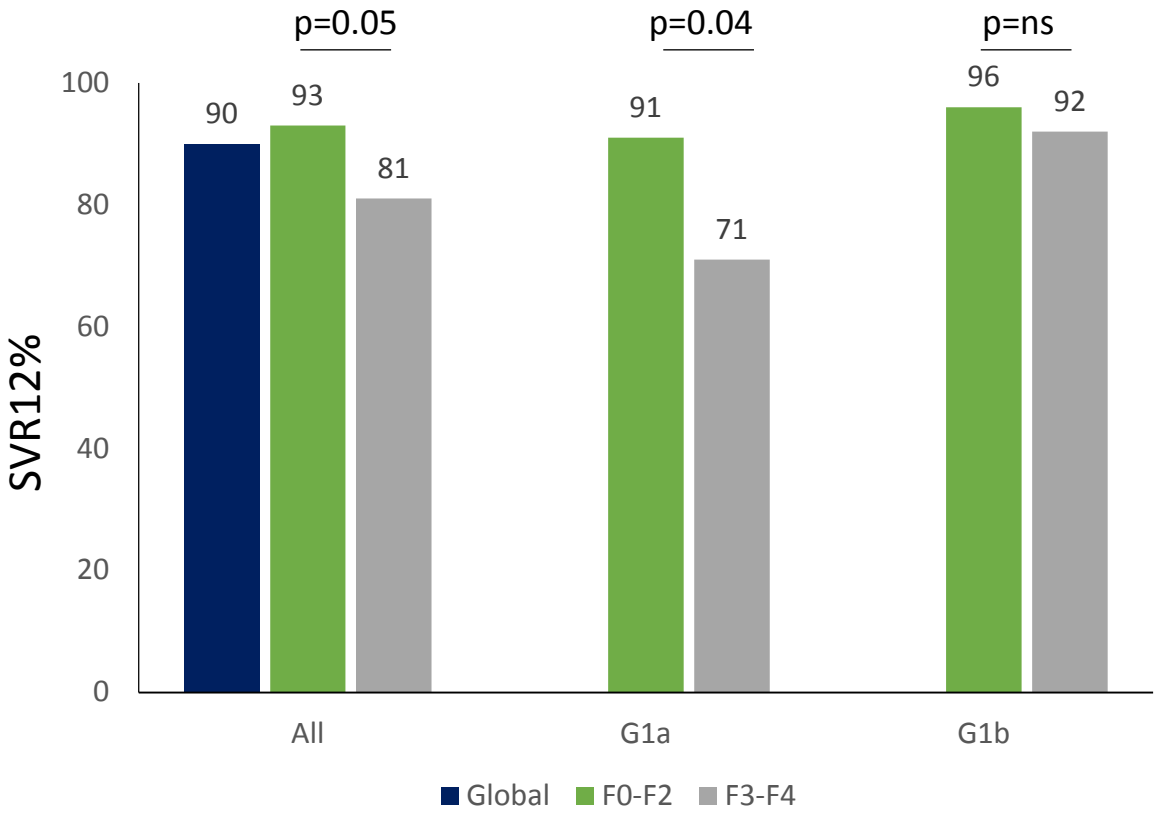
Ledipasvir/Sofosbuvir + RBV



Reddy et al , AASLD2014

Sofosbuvir + Simeprevir ± RBV

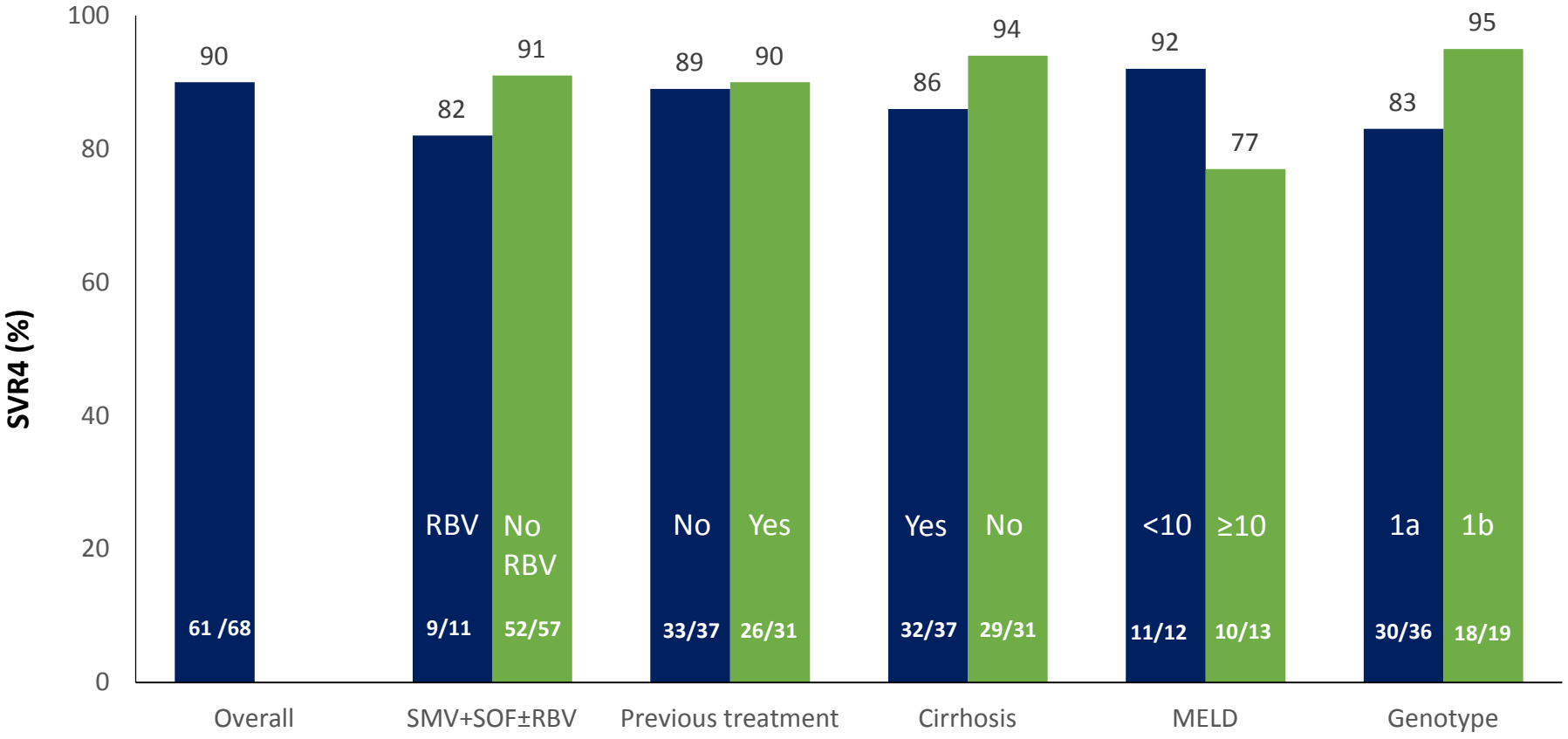
- 123 LT recipients
- 105 with SVR12 data
- 30% F3-F4
- 82% treatment-experienced
- 12% PI failure



Pungpapong et al, Hepatology 2015

Sofosbuvir + Simeprevir ± RBV

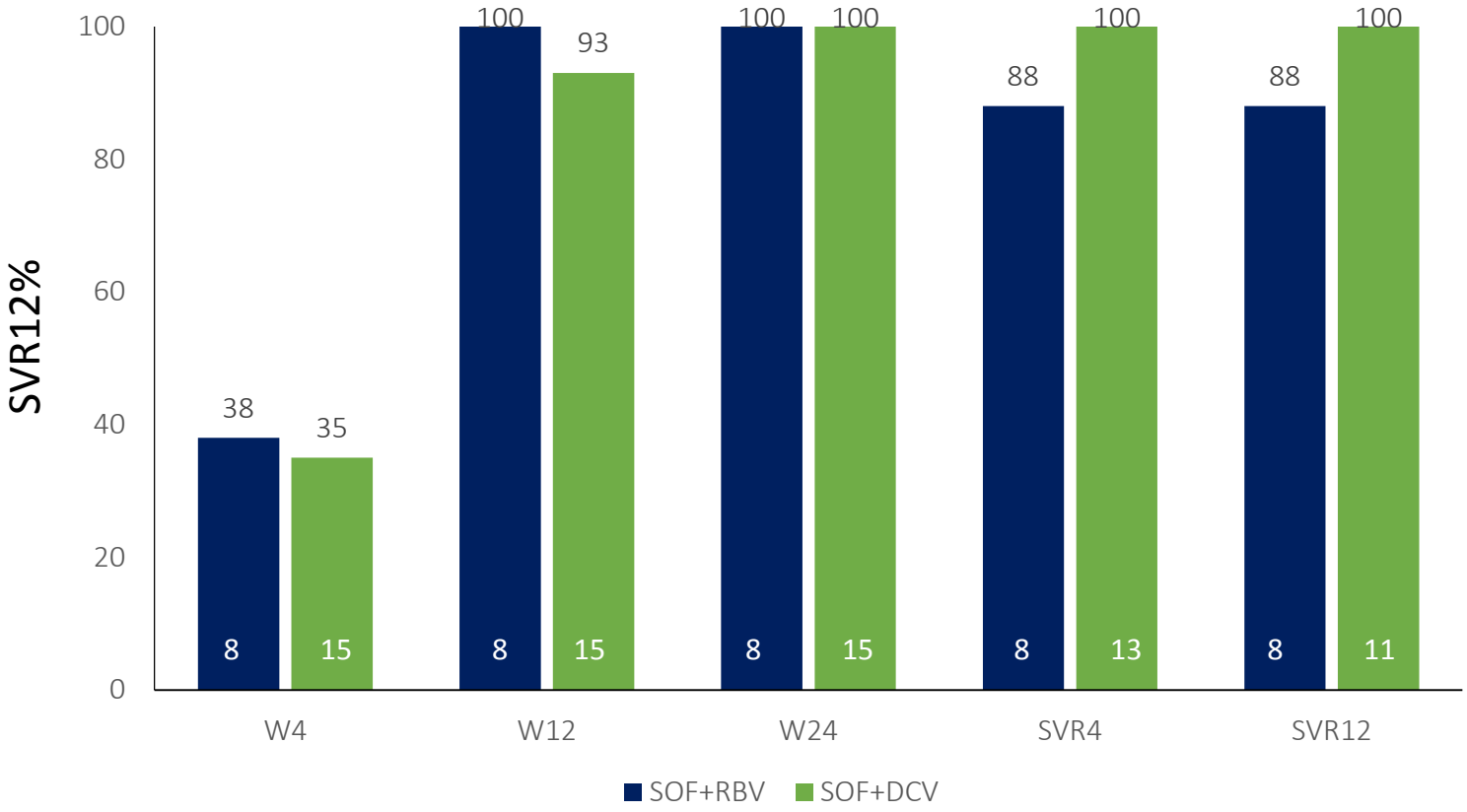
143 LT recipients, >60% with cirrhosis, >20% with MELD>10, including PI failures



Brown et al, AASLD 2014

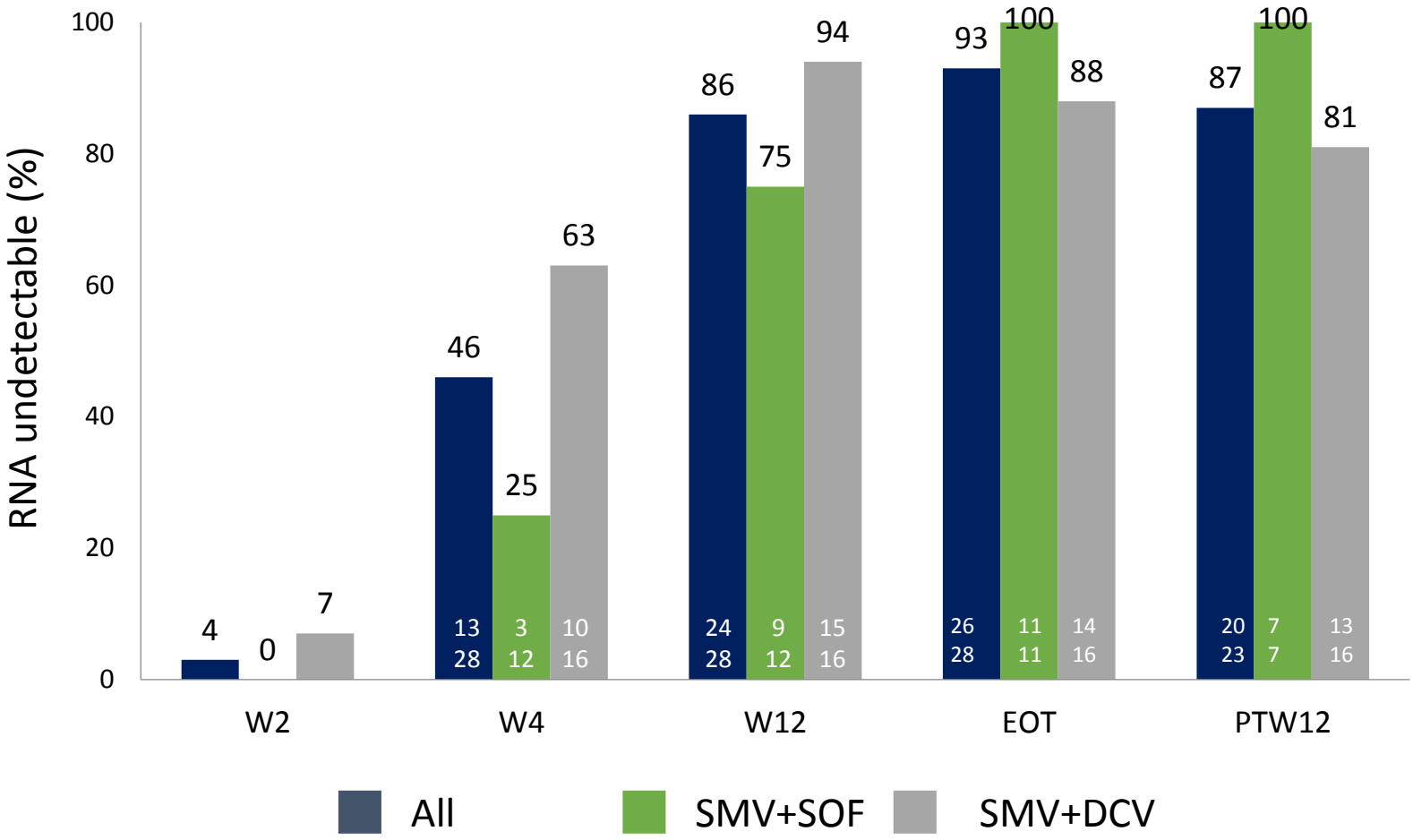
Sofosbuvir + Daclatasvir ± RBV

- CULPIT cohort, 23 patients with FCH



Leroy et al, AASLD 2014

Simeprevir + Daclatasvir ± RBV



Londoño, AASLD 2014

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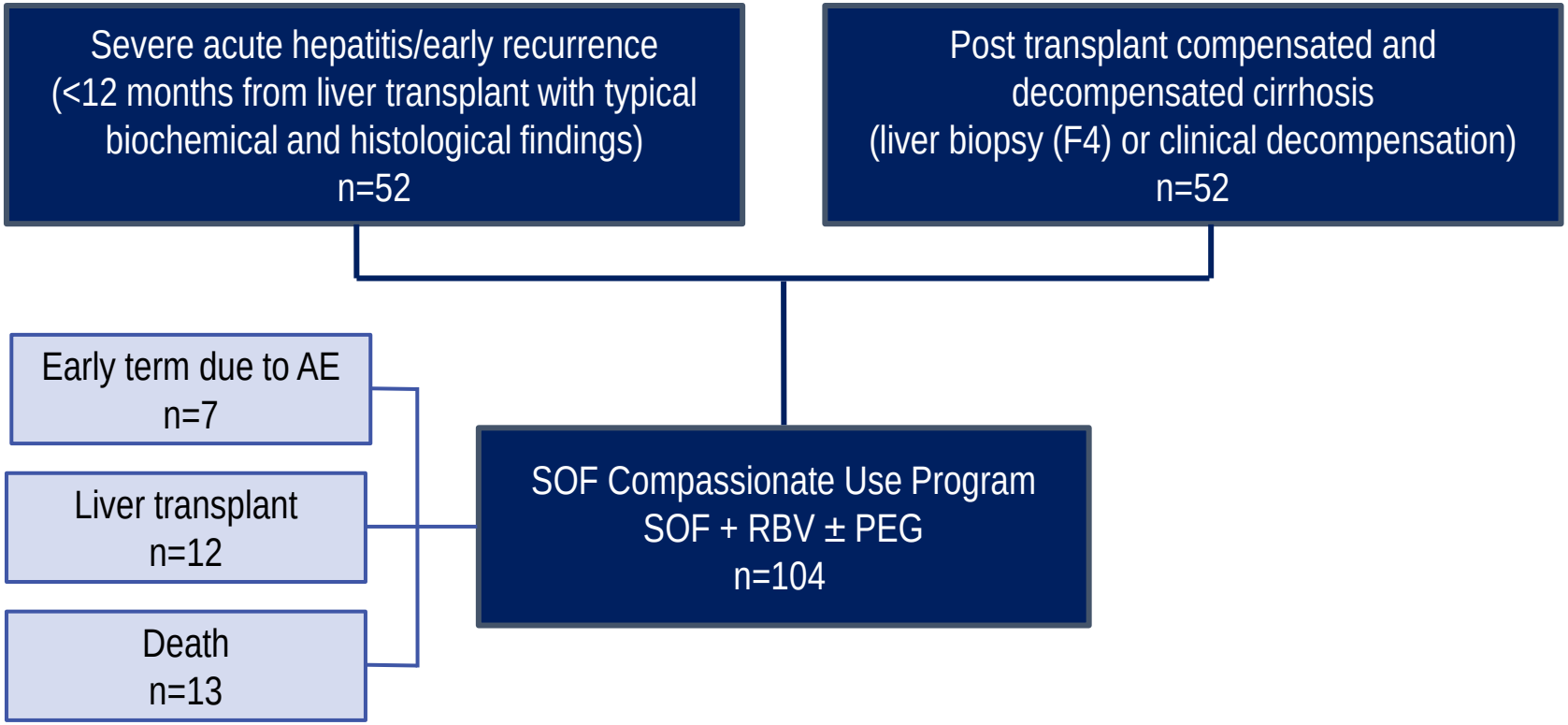
Treatment After Liver Transplant: Unsolved Issues

- Which is the right time to start antiviral therapy? Is pre-emptive therapy a good option?
- Is there a point where we might be able to eradicate HCV but not to revert liver cirrhosis (liver function, portal hypertension)?
- Which one is the best regimen?

Treatment After Liver Transplant: Unsolved Issues

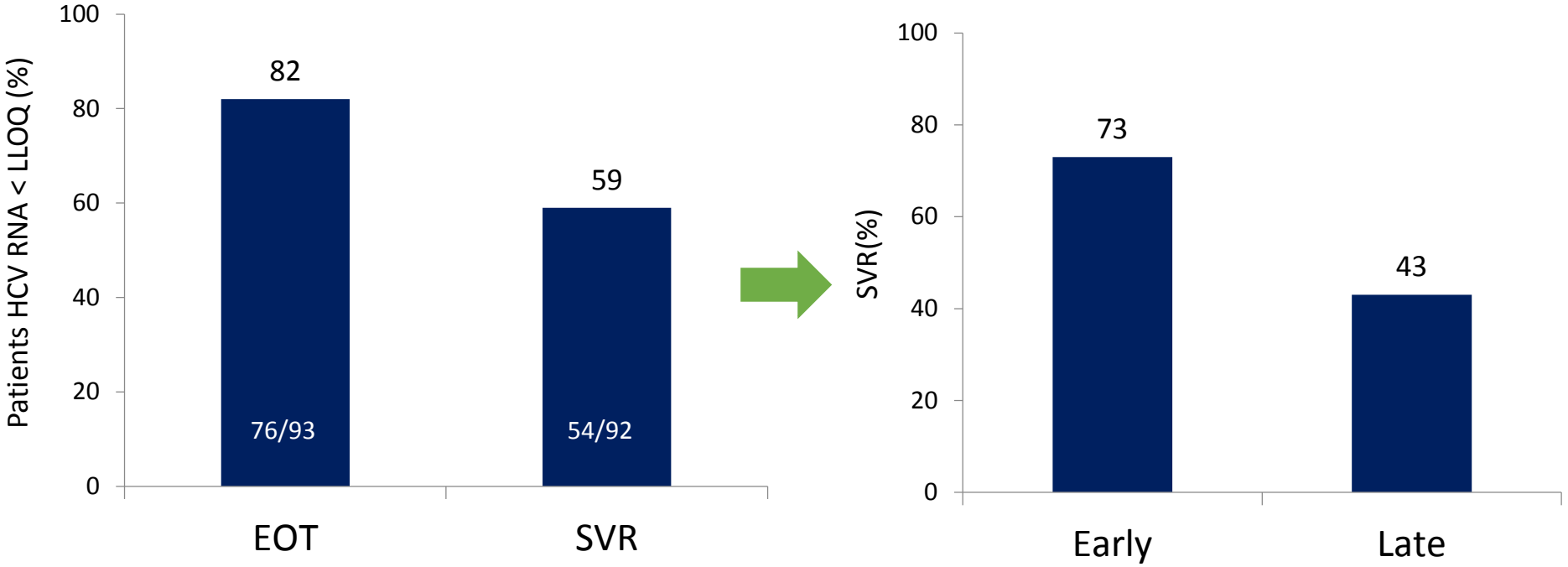
- Which is the right time to start antiviral therapy?



Forns, et al. Hepatology 2015

Treatment After Liver Transplant: Unsolved Issues

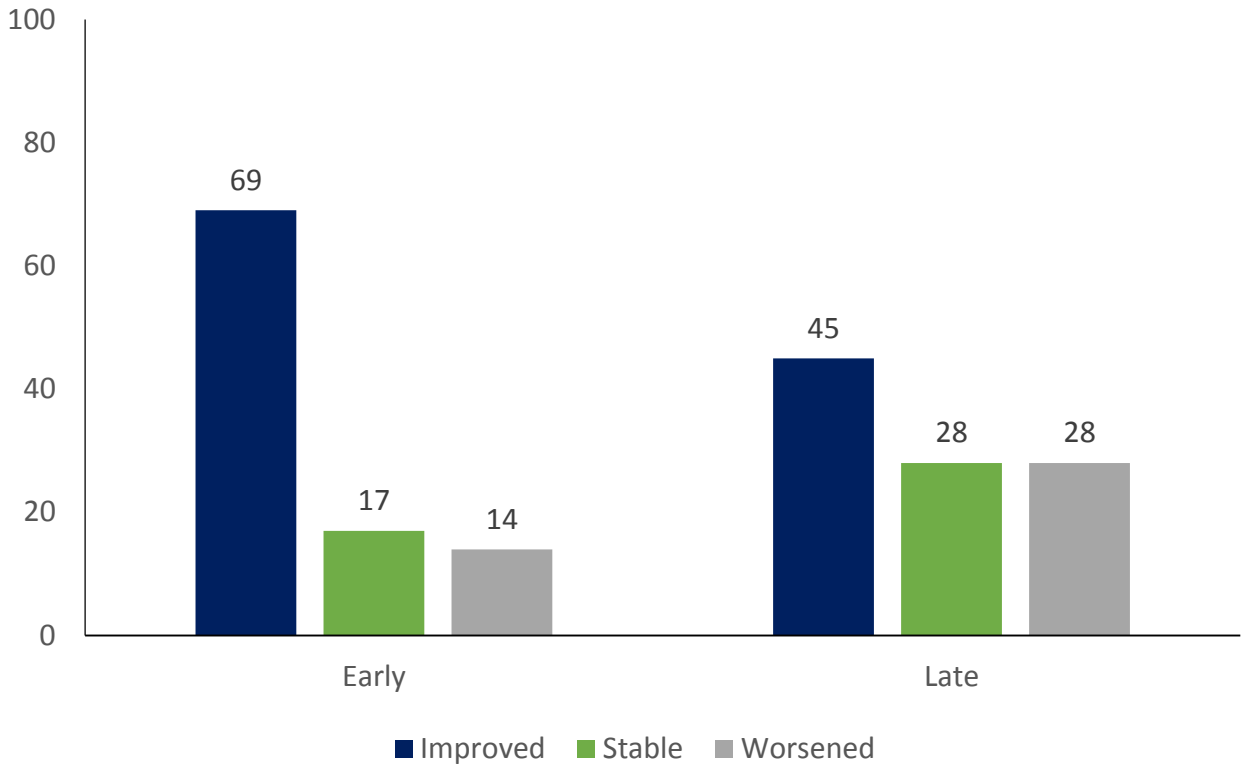
- Which is the right time to start antiviral therapy?



Forns, et al. Hepatology 2015

Treatment After Liver Transplant: Unsolved Issues

- Which is the right time to start antiviral therapy?



Forns, et al. Hepatology 2015

Treatment After Liver Transplant: Unsolved Issues

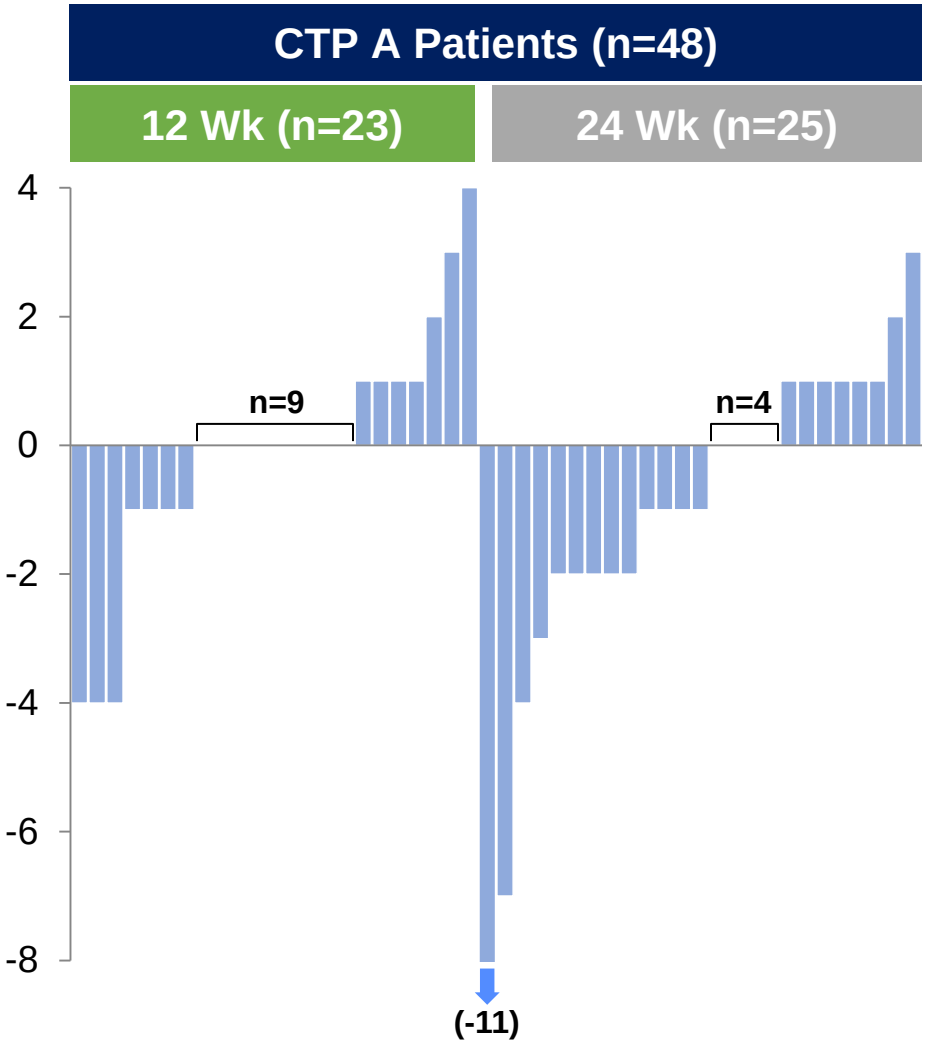
- Is pre-emptive therapy a good option?

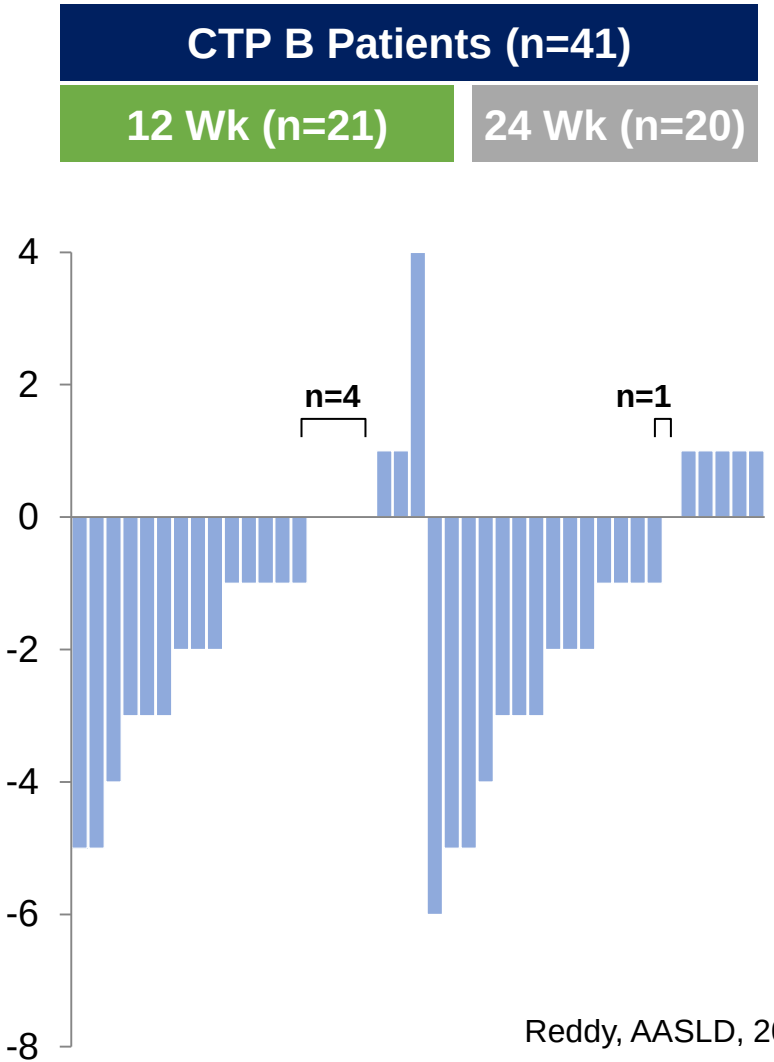
Type of therapy	Advantages	Disadvantages
Pre-emptive	1. It may prevent the infection of the graft 2. It may prevent the development of liver fibrosis	1. Difficult administration (renal function, potential for DDI, ability to take oral medications) 2. No data on safety and efficacy with DAAs.

Mariño, Londoño & Forns. Current Opinion in Organ Transplant, *accepted*

Treatment After Liver Transplant: Unsolved Issues

- Is there a no-return point?





Reddy, AASLD, 2014,

Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen?

- The degree of liver dysfunction
- Renal function
- Drug-drug interactions

Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen?

DRUG	METABOLISM/ ELIMINATION	CIRRHOSIS			RENAL FAILURE
		CTP-A	CTP-B	CTP-C	
Sofosbuvir	Kidney	yes	yes	yes	No if CrCl < 30 mL/min
Simeprevir	Liver	yes	yes	no	yes
Paritaprevir/r	Liver	yes	yes	no	yes
Ledipasvir	Liver	yes	yes	yes	yes
Ombitasvir	Liver	yes	yes	yes	yes
Daclatasvir	Liver	yes	yes	yes	yes
Dasabuvir	Liver	yes	yes	yes	yes

Treatment After Liver Transplant: Unsolved Issues

- Which one is the best regimen? Drug-drug interactions?

	Cyclosporine		Tacrolimus	
	Healthy volunteers	**Dose adjustment**	**Healthy volunteers**	**Dose adjustment**
Sofosbuvir	No change	Not necessary	No change	Not necessary
Simeprevir	↑ SMV 19%	Under investigation	↓17%	Not necessary
Daclatasvir	No change	Not necessary	No change	Not necessary
Ledipasvir	No change	Not necessary	No change	Not necessary
Paritaprevir/r	↑ 5.8 fold	↓ 5 fold	↑ 58 fold	↓ 100 fold

Gambato et al, J Hepatol 2014

Conclusions

- After liver transplantation, antiviral therapy administered in patients with mild fibrosis stages achieves higher response rates as compared to patients with cirrhosis and decompensation.

- The election of antiviral regimen should be based on patients characteristics (liver function, immunosuppression, renal function).

- The use of pre-emptive therapy needs further investigation.

- It is currently unknown if there is a no-return point in which antiviral therapy should not be administered.