HCV Treatment of Complicated Patients: Advanced Cirrhotics and Patients with Severe Renal Impairment

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HCV-infected Patients with Renal Impairment

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HCV and the Kidney

- HCV is associated with renal impairment
  - Mixed cryoglobulinemia
  - Non-glomerular renal diseases
- ESRD is 7 times higher in HCV versus non-HCV-infected patients
- HCV is associated with a higher risk (1.5 to 2.5 fold) of diabetes and cardiovascular/cerebrovascular disease

Corouge M, et al. *Liver Int*. 2016;36(suppl 1):28-33.

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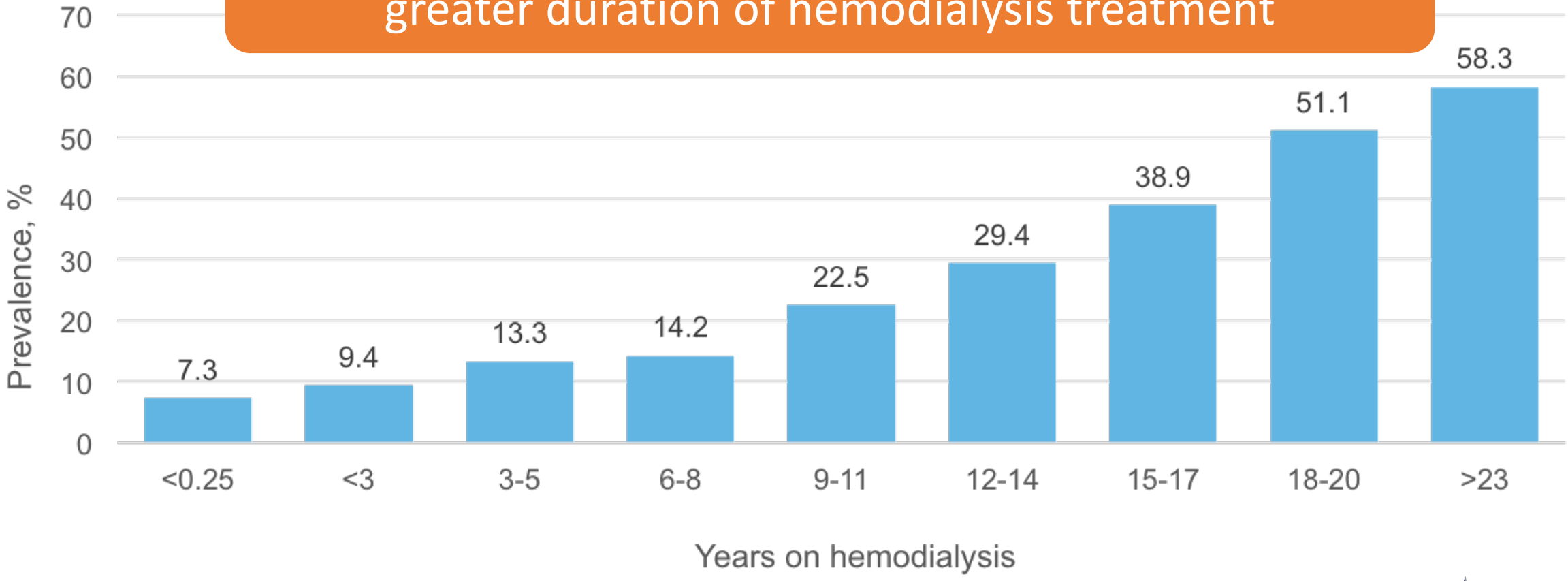
Time on Dialysis Is Correlated with HCV Infection

Increasing prevalence of HCV infection with greater duration of hemodialysis treatment



Dialysis patients from the Dialysis Outcome Practice Pattern Study (DOPPS)

Kalantar-Zadeh K, et al. *Int Urol Nephrol*. 2007;39:247-259.

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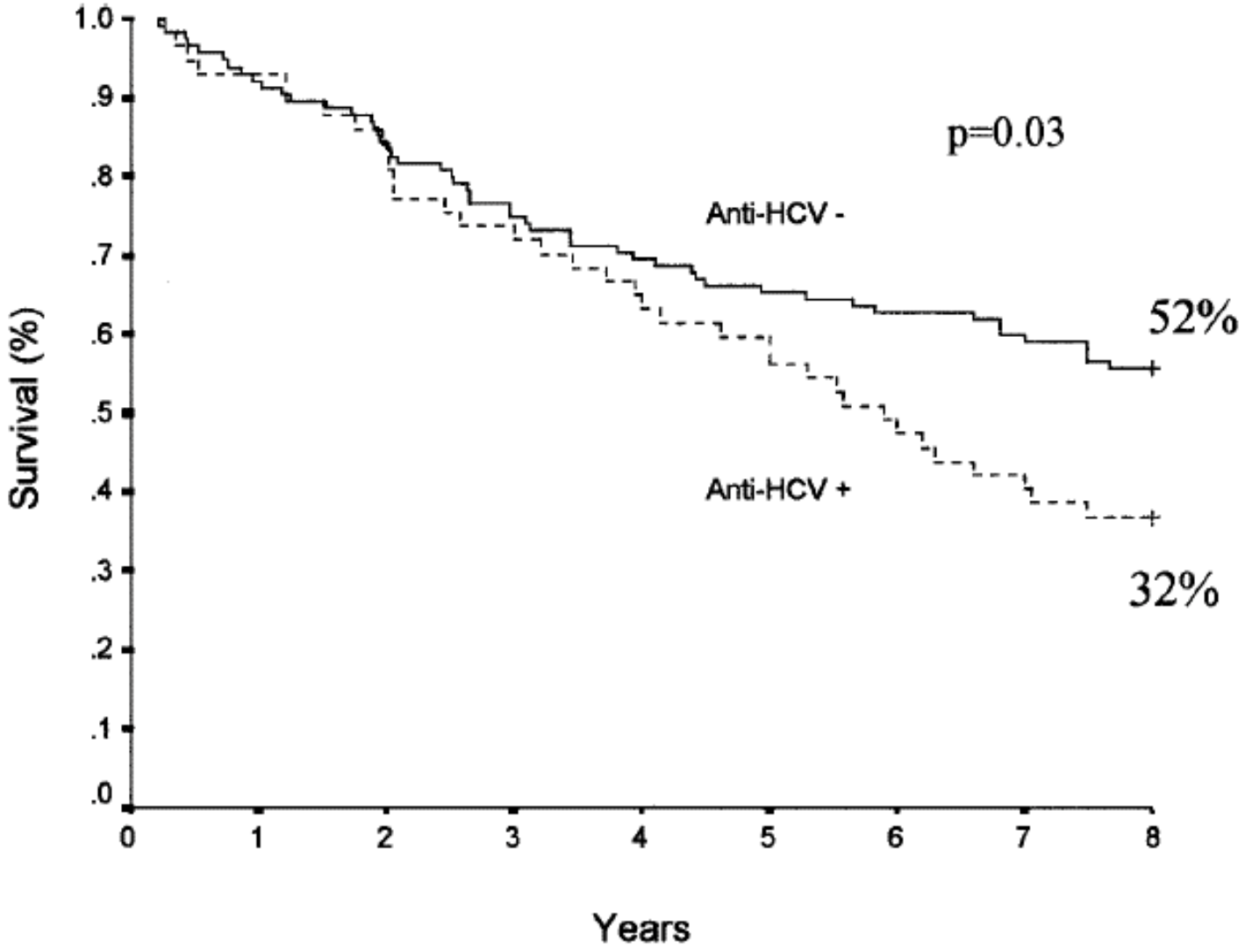
HCV and Risk of Death in Long-Term Hemodialysis Patients



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Sofosbuvir Pharmacokinetics in HCV-Negative Patients With Renal Impairment

Results After a Single-Dose of Sofosbuvir 400 mg

	Increase in AUC Relative to Subjects With Normal Renal Function (%)	
	Sofosbuvir AUC	**GS-3310007**
eGFR (mL/min/1.73 m^2)		
≥50 to <80	61	55
≥30 to <50	107	88
<30	171	451
ESRD requiring hemodialysis Dosed 1 hour Before hemodialysis After hemodialysis	 28 60	 1280 2070

Sofosbuvir full prescribing information.

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AASLD-IDSA Recommendations: Severe Renal Impairment or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Creatinine Clearance <30 mL/min
(Urgency to Treat or Retreat Is High and Renal Transplant is not an Immediate Option)

Genotype 1a	Elbasvir/grazoprevir (50/100 mg qd) for 12 weeks
Genotype 1b	Elbasvir/grazoprevir (50/100 mg qd) for 12 weeks Ombitasvir/paritaprevir/r (25/150/100 mg qd) + dasabuvir (250 mg bid) for 12 weeks
Genotype 4	Elbasvir/grazoprevir (50/100 mg qd) for 12 weeks

Creatinine Clearance <30 mL/min
(Treatment is Necessary and Transplantation Cannot be Performed)

Genotype 2, 3, 5, 6	PegIFN and dose-adjusted RBV† at 200 mg/day

AASLD-IDSA. http://www.hcvguidelines.org/full-report-view. March 14, 2017.

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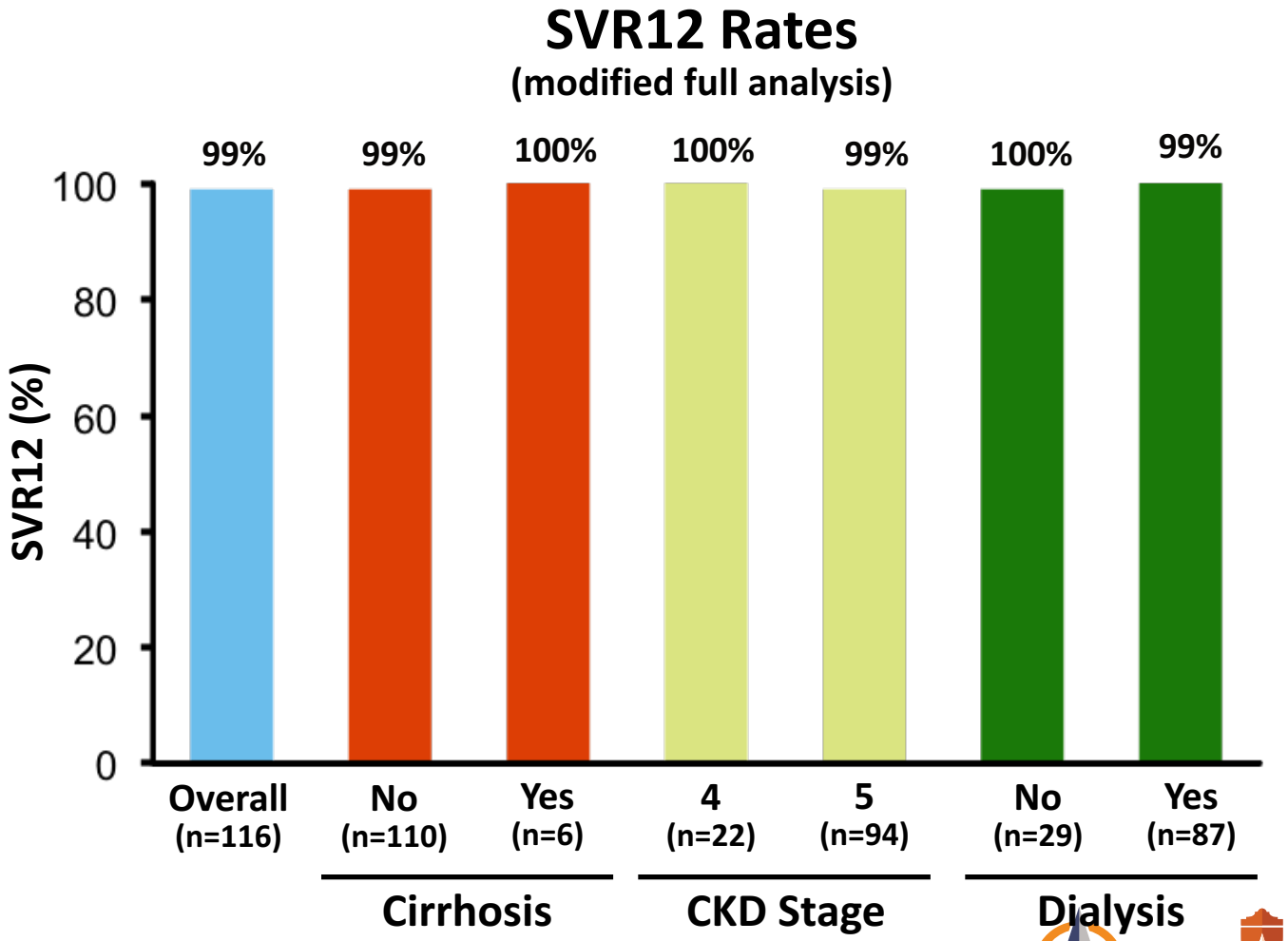
C-SURFER: SVR12 Rates With 12 weeks Elbasvir/Grazoprevir in HCV G1, Stage 4/5 CKD

Phase 3

- Placebo-controlled
- Genotype 1
- Treatment-naïve and Treatment-experienced
- CKD stage 4/5 (+ hemodialysis)
- Compensated cirrhosis allowed



Roth D, et al. *Lancet*. 2015;386:1537-1545.

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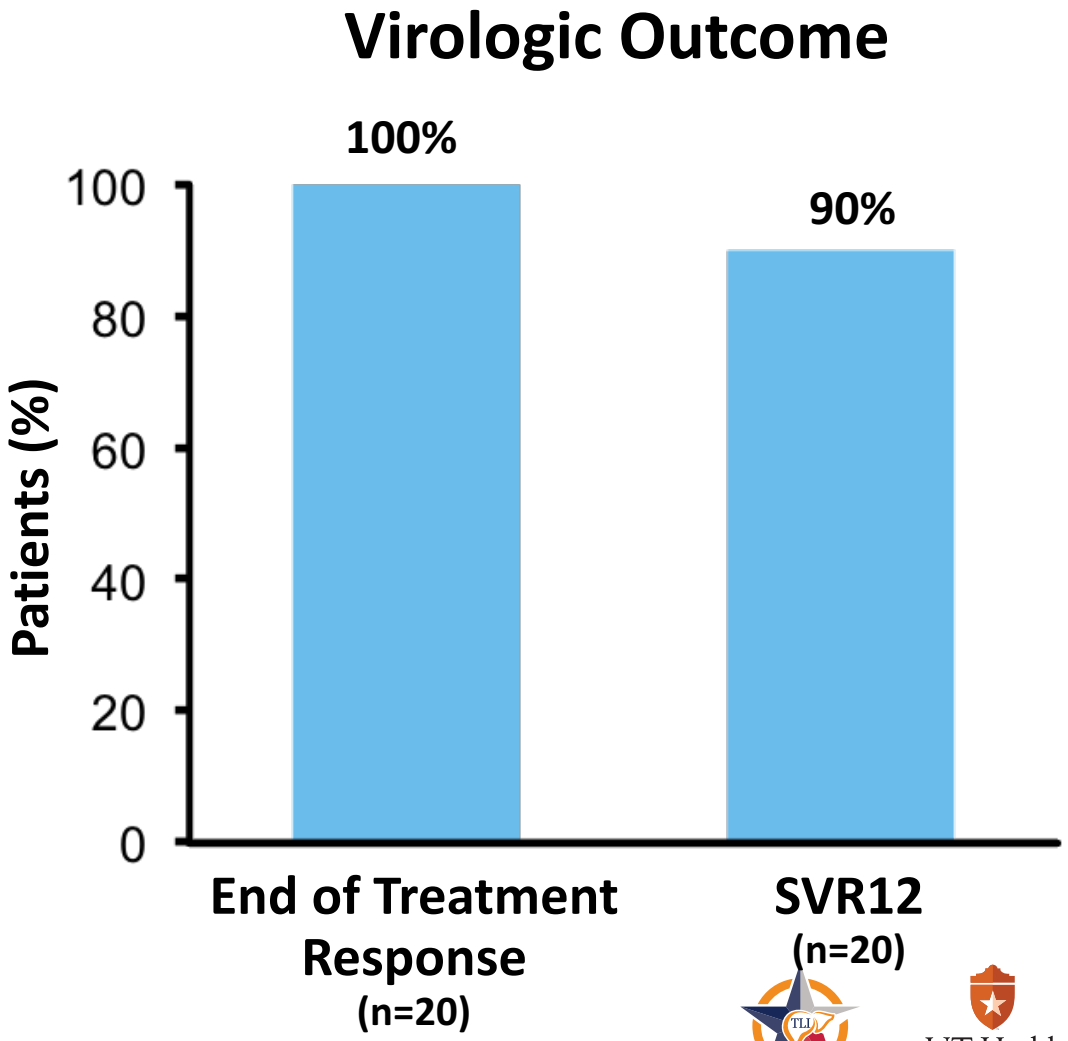
RUBY-1: Ombitasvir/Paritaprevir/r + Dasabuvir ± RBV in Severe Renal Impairment or ESRD

- RBV dose interruption (8/13)
  - Erythropoietin administration (n=4)
  - No discontinuations due to adverse events
  - Hemoglobin <8 g/dL (n=1)
    - No other grade 3/4 laboratory abnormalities
  - No clinically significant changes in liver or renal function markers



Pockros PJ, et al. *Gastroenterology*. 2016;Mar 11. [Epub ahead of print].

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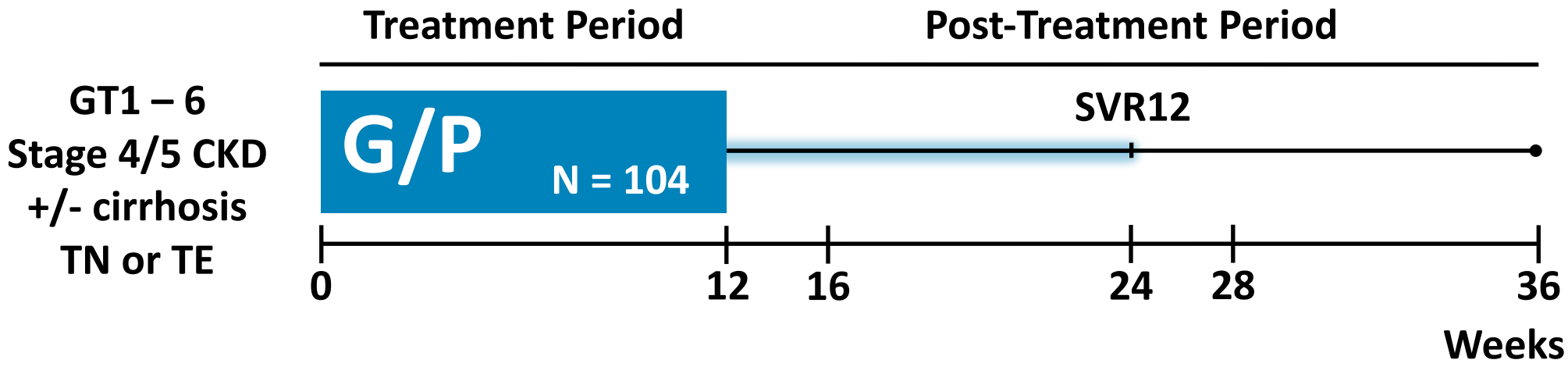
EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults with Renal Impairment and GT1 – 6 Infection



- GT1: 52%, GT2: 16%, GT3: 11%, GT4-6: 21%
- Treatment naïve: 58%
- Compensated cirrhosis: 19%
- CKD Stage 4: 12%, Stage 5: 88%, 82% on hemodialysis

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

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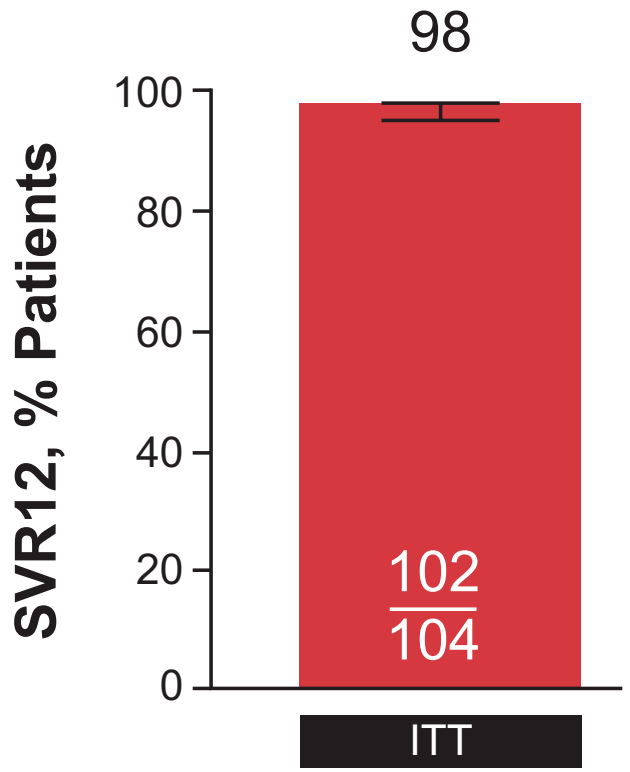
EXPEDITION-IV: Results – SVR12 by Intent-to-treat (ITT) Analysis



	ITT
Breakthrough	0
Relapse	0
Discontinuation	1
LTFU	1

mITT = 100% SVR12

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

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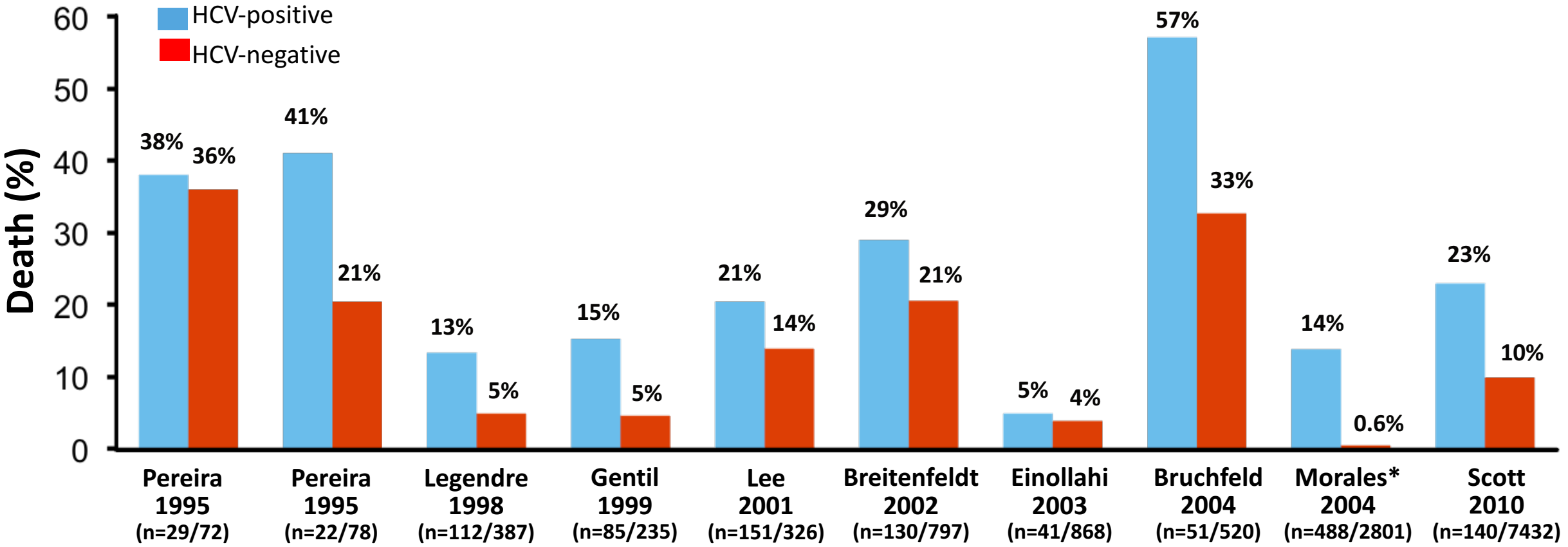
Death Rate in HCV+ Versus HCV- Patients After Kidney Transplantation



*Proportion of deaths due to liver disease.
Post-transplant follow-up ranged from 57 to 130 months (2 studies did not report follow-up duration).
Carbone M, et al. *Transplantation*. 2013;95:779-786.

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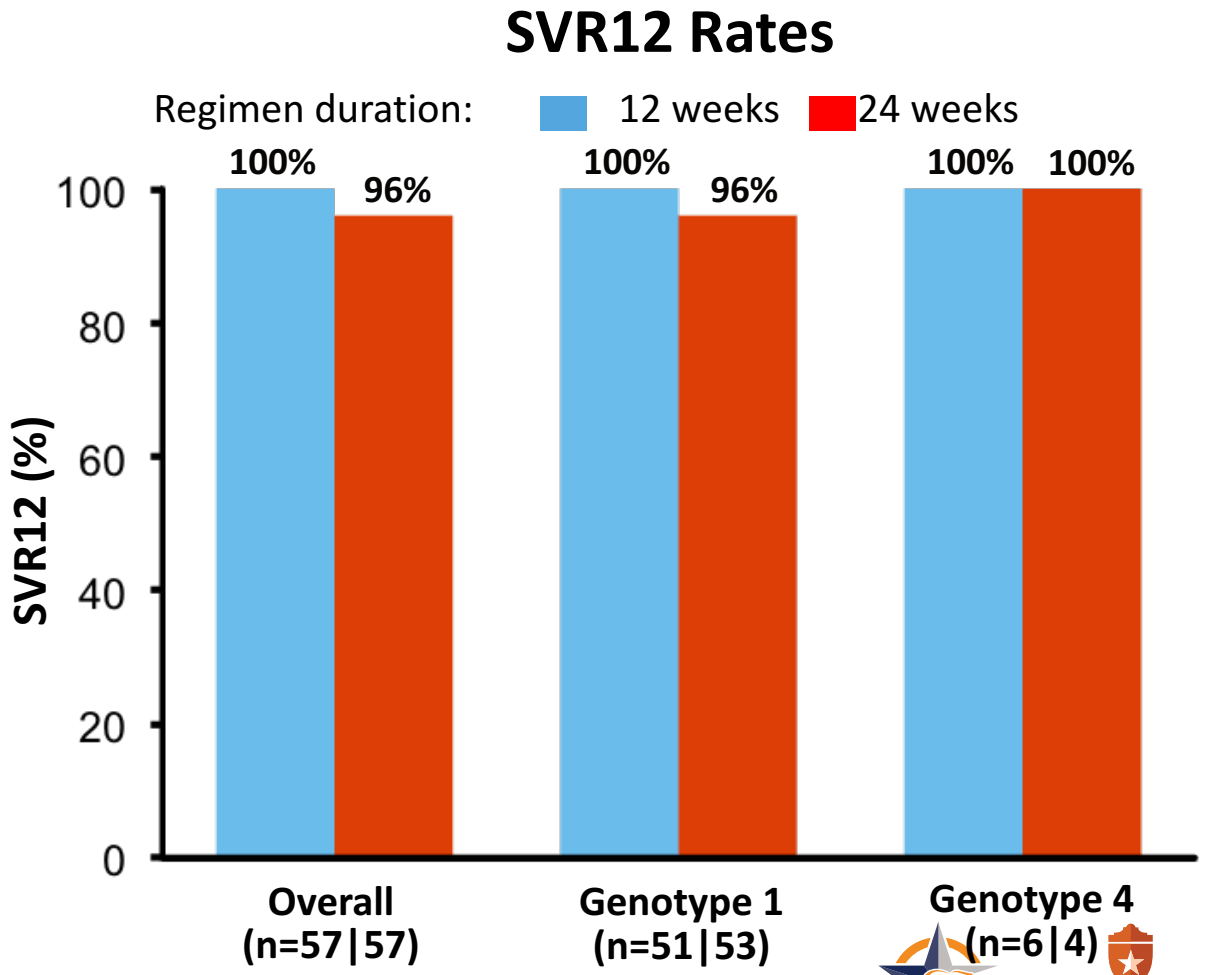
Ledipasvir/Sofosbuvir for Kidney Transplant Recipients With HCV Genotype 1 or 4

- 12 vs. 24 weeks
- No virologic failures
- Safety
  - Discontinuations due to adverse events: <1%
  - eGFR <30 mL/min during therapy: 4% (4/114; related to treatment in 1 patient)
  - No episodes of rejection
  - No clinically meaningful reductions in renal function



Colombo M, et al. *J Hepatol*. 2016;64(suppl 2):S183. Abstract GS13.

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Use of HCV-Positive Donor Kidneys

- Controversy
  - Viral transmission is invariable
  - Genotype superinfection can occur
  - Patient and allograft survival may be inferior compared with HCV-positive recipients of HCV-negative donor kidneys (based on historical data with IFN-based therapy)
- Justification
  - HCV-positive ESRD patients are afforded a longer life expectancy from transplantation with an HCV-positive donor kidney than remaining on dialysis
  - Does not increase frequency of progressive liver disease and liver failure
  - Increase pool of donor organs
  - Similar 10-year survival rates for HCV-positive and HCV-negative donor kidneys
  - 73% versus 77% (P=0.2)

Sawinski D, et al. *Transplantation*. 2015;99:2458-2466; Morales JM, et al. *Am J Transplant*. 2010;10:2453–2462.

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Patients With Cirrhosis: What Options Exist?

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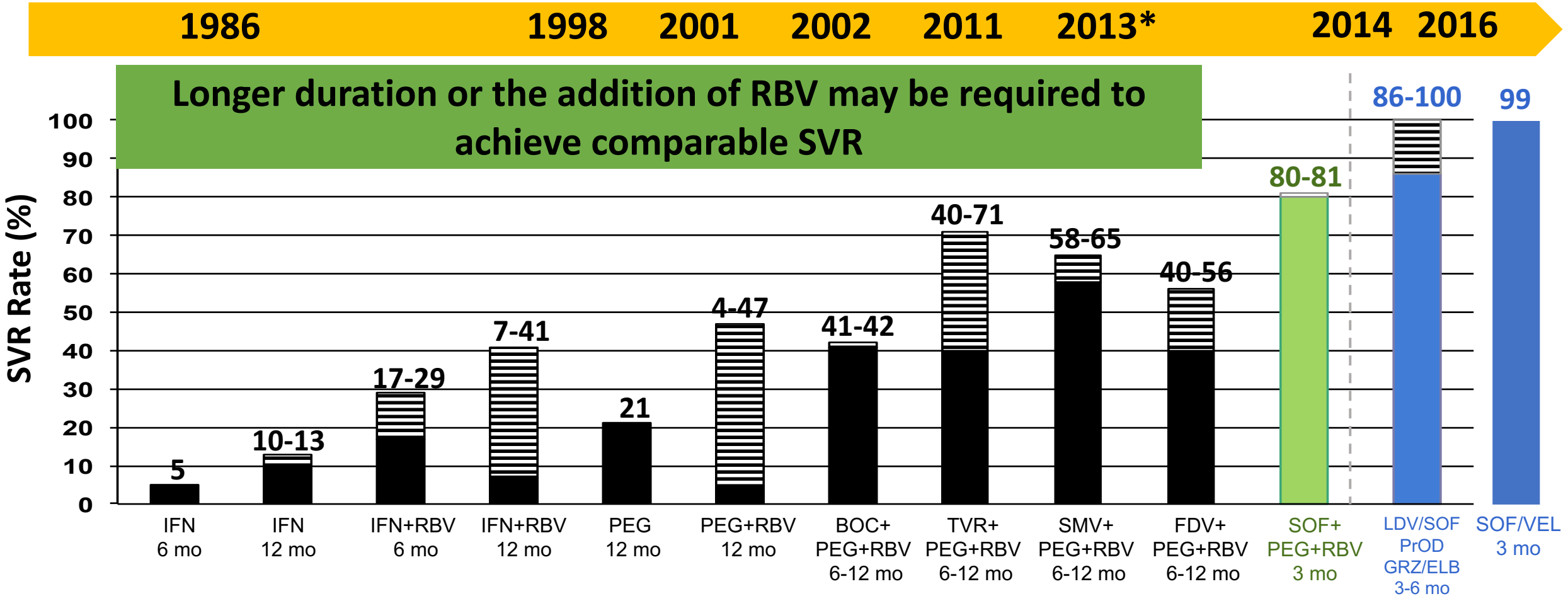
SVR Rates in HCV GT 1 TN or TE with Bridging Fibrosis-Cirrhosis



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Natural History of Cirrhosis

Stage	Definition	1-year mortality	Median Survival
1	Compensated **without varices**	1%	>12 years
2	Compensated **with varices**	3%	
3	Decompensated with ascites **without variceal hemorrhage**	20%	~2 years
4	Decompensated with/out ascites **with variceal hemorrhage**	57%	

D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*. 2006;44:217-231.

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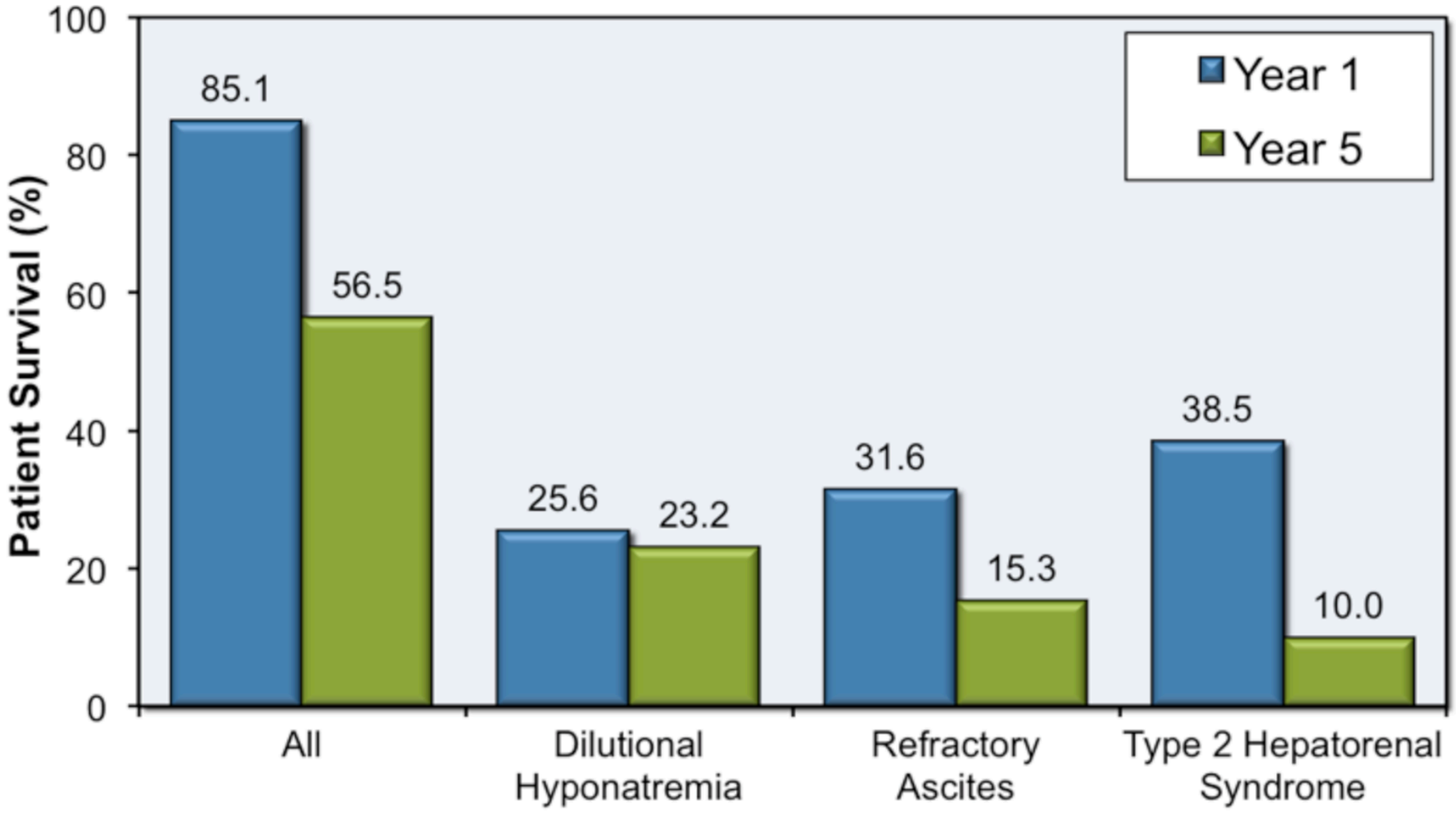
Natural History and Survival of Patients with Ascites



Planas R, Montoliu S, Ballesté B, Rivera M, Miguel M, Masnou H, Galeras JA, Giménez MD, Santos J, Cirera I, Morillas RM, Coll S, Solá R. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin Gastroenterol Hepatol*. 2006; 4:1385-94.

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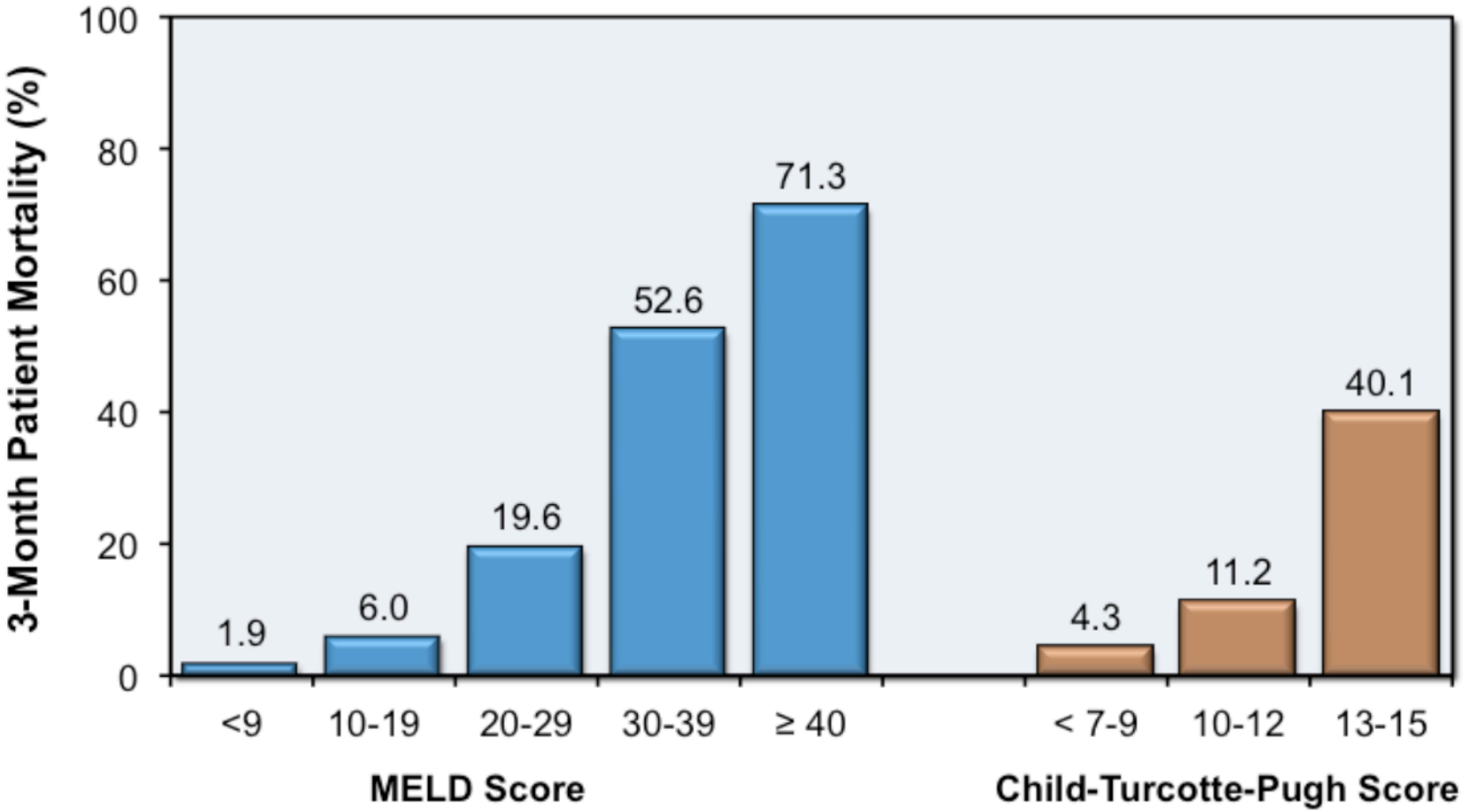
3 Month Mortality



Guidelines recommend referral for liver transplant with a MELD $\geq$ 10 or CTP score $\geq$ 7

Wiesner R. *Gastroenterology*. 2003;124:91-6.

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Dose Adjustments in Cirrhosis

Childs Class	PEG	Ribavirin Daily	Simeprevir	PrOD
A	Standard	1000-1200 mg/day	150 mg	75/50/12.5 mg + 250 mg
B	No	600 mg	No	No
C	No	600 mg	No	No

Childs Class	Elbasvir/ grazoprevir	Sofosbuvir/ velpatasvir	Ledipasvir/ sofosbuvir	Daclatasvir
A	50/100 mg	400mg/100mg	90mg/400mg	60 mg
B	No	400mg/100mg	90mg/400mg	60 mg
C	No	400mg/100mg	90mg/400mg	60 mg

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Decompensated Cirrhosis: Limited Options

Childs Class	PEG	Ribavirin Daily	Simeprevir	PrOD
A	nda	1000-1200 mg/day	50 m	75/50/ 5 m 250 mg
B		600 mg		
C	No	600 mg	No	No

Childs Class	Elbasvir/ grazoprevir	Sofosbuvir/ velpatasvir	Ledipasvir/ sofosbuvir	Daclatasvir
A	/10	400mg/100mg	90mg/400mg	60 mg
B		400mg/100mg	90mg/400mg	60 mg
C	No	400mg/100mg	90mg/400mg	60 mg

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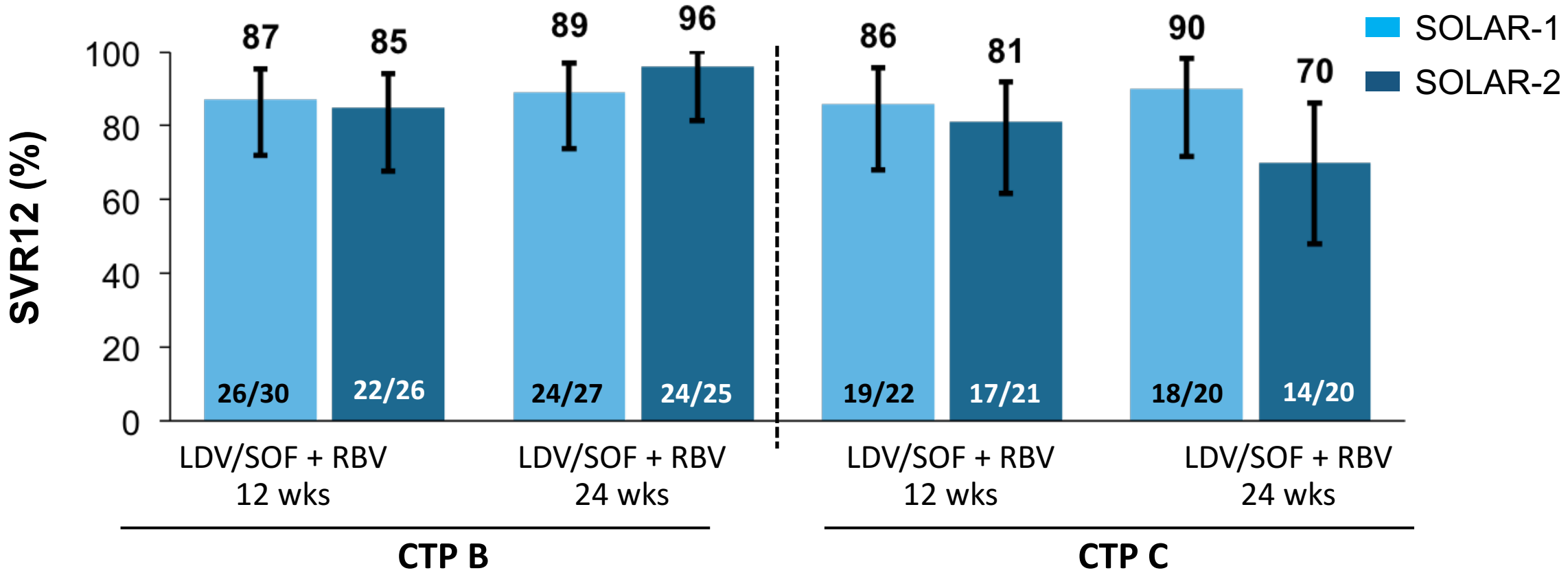
Overall Efficacy Pre-Transplant in GT 1 and GT4

SOLAR-1 and SOLAR-2: LDV/SOF + RBV in Decompensated Cirrhosis



Comparable efficacy between SOLAR-1 and SOLAR-2 studies

Charlton *Gastroenterology*. 2015. Volume 149, Issue 3, Pages 649–659.

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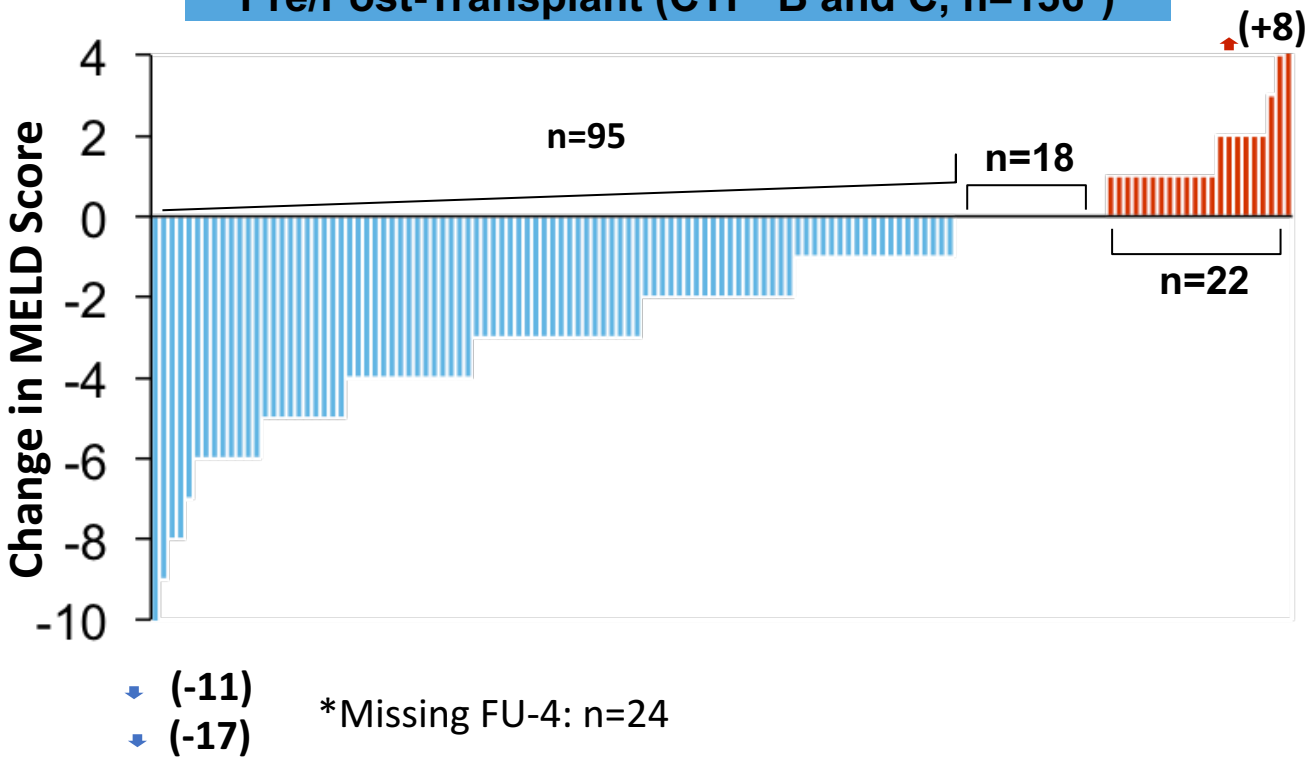
Liver Function Change: Baseline to Follow-Up Wk 4

SOLAR-2: LDV/SOF + RBV in Decompensated and Post-Liver Transplant Patients

MELD Score Change

Pre/Post-Transplant (CTP B and C, n=136*)



*Missing FU-4: n=24

Change in CTP Class

		Baseline CTP		
		A (5–6) n=73	B (7–9) n=100	C (10–12) n=54
Follow-up Week 4 CTP	A (5–6)	67 (96)	31 (35)	2 (5)
	B (7–9)	3 (4)	57 (65)	20 (48)
	C (10–12)	0	0	20 (48)

no assessment: CTP A, n=3; CTP B, n=12; CTP C, n=12

Majority showed improvements in MELD and CTP scores

Manns MP et al, *Lancet Infect Dis.*, 2016 Jun;16(6):685-97.

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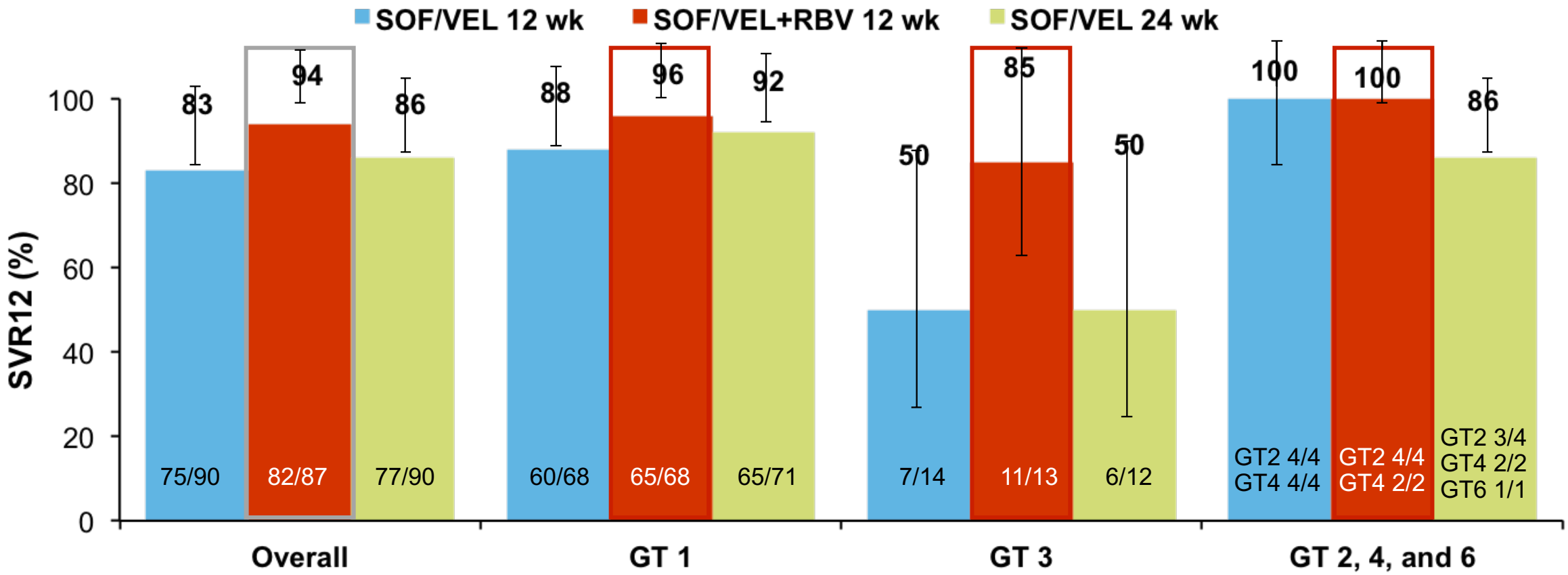
SOF/VEL in HCV Decompensated Cirrhosis



N Engl J Med. 2015. Dec 31;373(27):2618-28.

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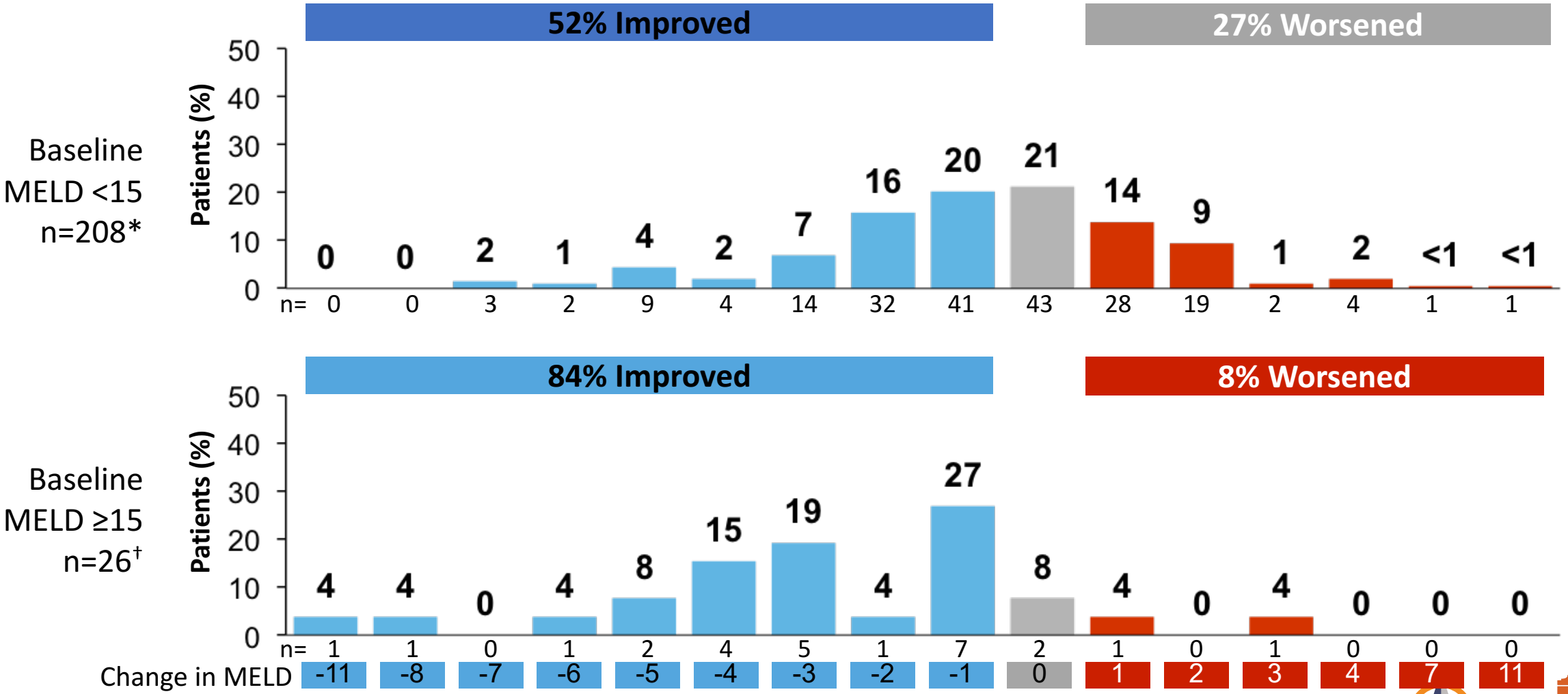
MELD Change (Baseline to FU12)

ASTRAL-4: Subjects with SVR12, Overall



No follow-up Week 12 assessment for *5 patients, †0 patients.

N Engl J Med. 2015. Dec 31;373(27):2618-28.

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Conclusions

- HCV remains challenging to treat with chronic kidney disease, especially in those non-G1/4
- All-oral therapy has very high efficacy in compensated cirrhosis
- Treatment of decompensated HCV remains controversial

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