A 55 year old man with cirrhosis due to chronic hepatitis C (CHC) genotype 3a is referred for liver transplantation.

Three years ago he was treated with 24 weeks of peginterferon alfa-2a (180 µg/wk, PEGIFN) plus ribavirin (400 mg bid, RBV). At that time his evaluation revealed Hgb 14 g/dL, WBC 5300/µL, Platelets 132,000/µL, bilirubin 1.2 mg/dL, albumin 4.3 g/dL, INR 1.1, creatinine 0.8 mg/dL, and baseline HCV RNA 1,757,530 IU/mL. Liver ultrasonography was normal and liver biopsy showed grade 2 inflammation and stage 4 fibrosis. He required erythropoietin analogue for anemia and received Lexapro® for depression in the last two months of treatment. The blood level of HCV RNA was 160 IU/mL at treatment week 12, <43 IU/mL at end-of-treatment week 24, and 1,330,000 IU/mL at post-treatment week 12.

At presentation, he described severe fatigue, ankle swelling, ascites that was well controlled with diuretics, and mild encephalopathy that was controlled with rifaximin. A prior EGD showed Grade II varices that were banded. He denied jaundice, variceal bleeding, or encephalopathy.

Past Medical History included chronic back pain with ongoing narcotic use, and past, but not current, smoking.

Medications and OTC supplements: Spironolactone 50 mg/d, Furosemide 20 mg/d, Rifaximin 550 mg bid, Prilosec 20 mg bid, and fentanyl patch, oxycodone, milk thistle, fiber supplement, fish oil and a multivitamin tablet.

Physical Examination: BP 141/77, P 102, T 36.9˚C, BMI 27, RR 16, and SpO2 95% on room air. He was alert, oriented, well-developed and well-nourished. He lacked jaundice but had scattered spider telangiectasia, hepatosplenomegaly with firm liver edge, and minimal bilateral lower extremity edema. There was no ascites, confusion, or asterixis.

Laboratory tests indicated WBC 5100/µL, Hgb 16.9 g/dL, Platelets 91,000/µL, ALT 61 IU/mL, AST 66 IU/mL, Alkaline Phosphatase 104 IU/mL, Bilirubin 2.0 mg/dL, Albumin 3.1 g/dL, creatinine 0.7 mg/dL, and INR 1.5. HCV RNA was 4,770,000.

TP CT showed trace ascites and liver heterogeneity with multiple transient hypervascularities.

Summary

- HCV genotype 3a infection
- Treatment experienced (PEG/RBV)
  - Anemia
  - Depression
- Cirrhosis
  - Child-Turcotte-Pugh score is 9 (CTP class B)
  - MELD score 14
  - Splenomegaly, thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia
- Alcohol history
- Prescription narcotic use

For Discussion

- Severity of liver disease (CTP B)
- Transplant candidacy
- Treatment Options
  - Genotype 3a
  - CTP B
  - Treatment experienced
- Alcohol history
- DDIs

How does severity of liver disease influence your decision to treat or not to treat with DAAs?

Is there a point of “no return”?

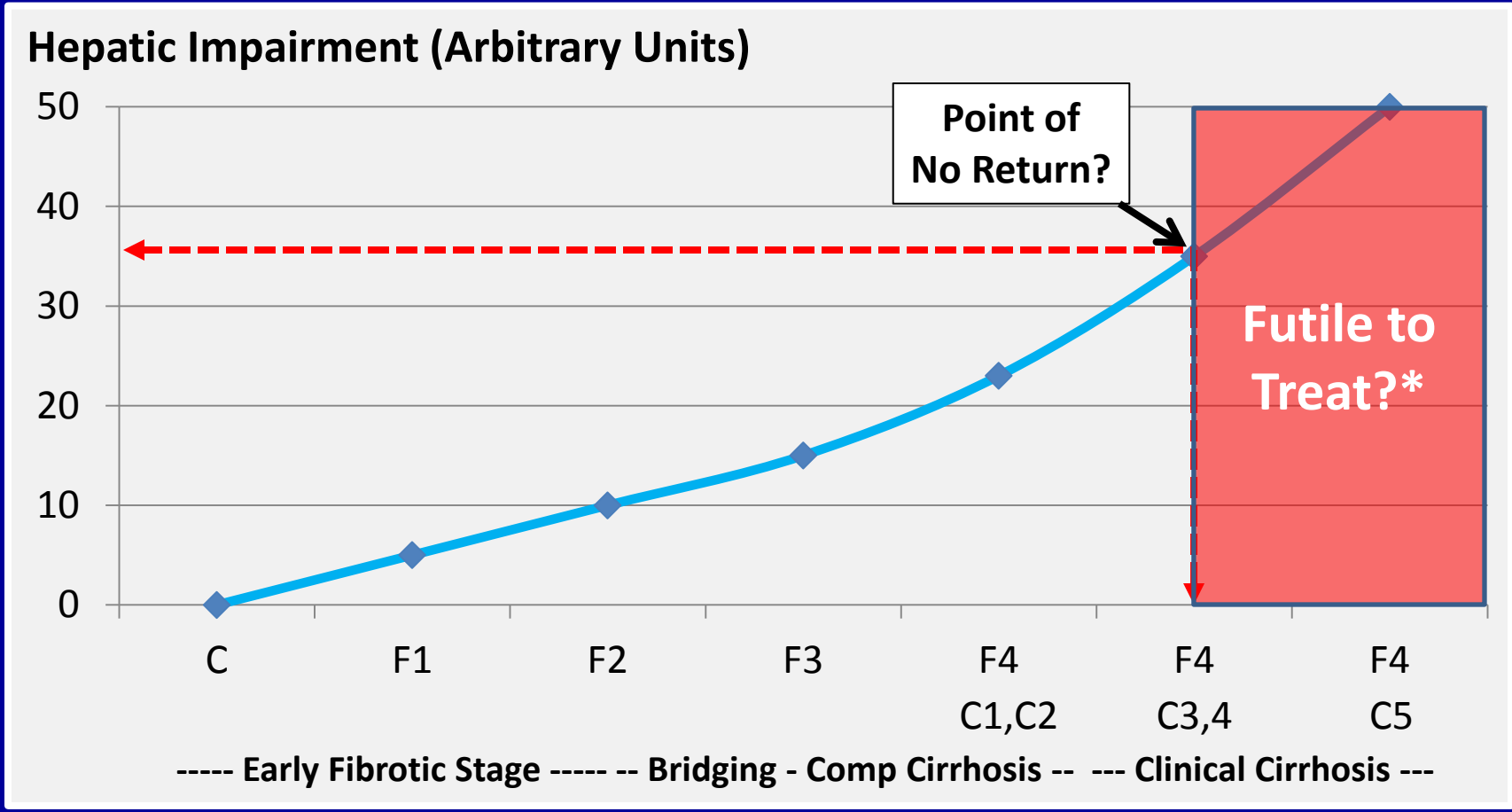
Does this data influence your Rx decision?

CUPIC: Rx of HCV GT1 Cirrhosis with PI-based Triple Therapy

Albumin		Platelet Count μL^{-1}	
		> 100,000	≤ 100,000
≥ 3.5 g/dL	N	306	74
	% SVR	**55%**	37%
	% SAE/Death	6%	12%
< 3.5 g/dL	N	31	37
	% SVR	29%	27%
	% SAE/Death	16%	**51%**

Hezode C, et al. Effectiveness of Telaprevir or Boceprevir in Treatment-experienced Patients with HCV Genotype 1 Infection and Cirrhosis. Gastroenterology 2014;147:132-142.

Is there a "Point of No Return"?



Disease Progression (from Healthy (C) to Severe Decomp (C5)

* Achieving SVR would not change clinical outcome. Only reason to treat would be to achieve pTVR.

How do you define “Point of No Return”?

Available Test or Model	“Point of No Return” ???
• CTP class	➢ A-, B+, B, B-, C+, C, or C-
• CTP score	➢ 6, 7, 8, 9, 10, 11, 12, 13-15
• MELD	➢ 10, 15, 20, 25, 30, 35, 40
• Serum Biomarkers	➢ FibroTest > 0.73, 0.8, 0.9, 1
• Elastography	➢ FibroScan > 12.5, 15, 18, 20
• HVPG	➢ 6, 10, 15, 20, 25, 30
• Other?	➢ Other?

Does liver transplant (LT) candidacy influence your decision to treat or not to treat with DAAs?

Would you treat pre- or post-LT?

Table 1 Current status of liver transplantation for diagnosis of HCV snapshot of waiting list on May 3, 2013

MELD[a] or status	Recipient diagnosis		Total	Total proportion of HCV cases[c]	Distribution of MELD scores[d]	
	No HCV diagnosis[b]	HCV diagnosis				
	N	N	N	%	No HCV	HCV
MELD: 6-10	2953	1550	4503	34.4 %	28.6 %	27.0 %
MELD: 11-15	2307	1328	3635	36.5 %	22.4 %	23.2 %
MELD: 16-20	1374	763	2137	35.7 %	13.3 %	13.3 %
MELD: 21-25	1257	661	1918	34.5 %	12.2 %	11.5 %
MELD: 26-30	351	248	599	41.4 %	3.4 %	4.3 %
MELD: 30+	148	83	231	35.9 %	1.4 %	1.4 %
Inactive	1926	1102	3028	36.4 %	18.7 %	19.2 %
Total	**10317**	**5735**	**16052**	**35.7 %**		

Removals from waiting list for death/too sick and liver transplants

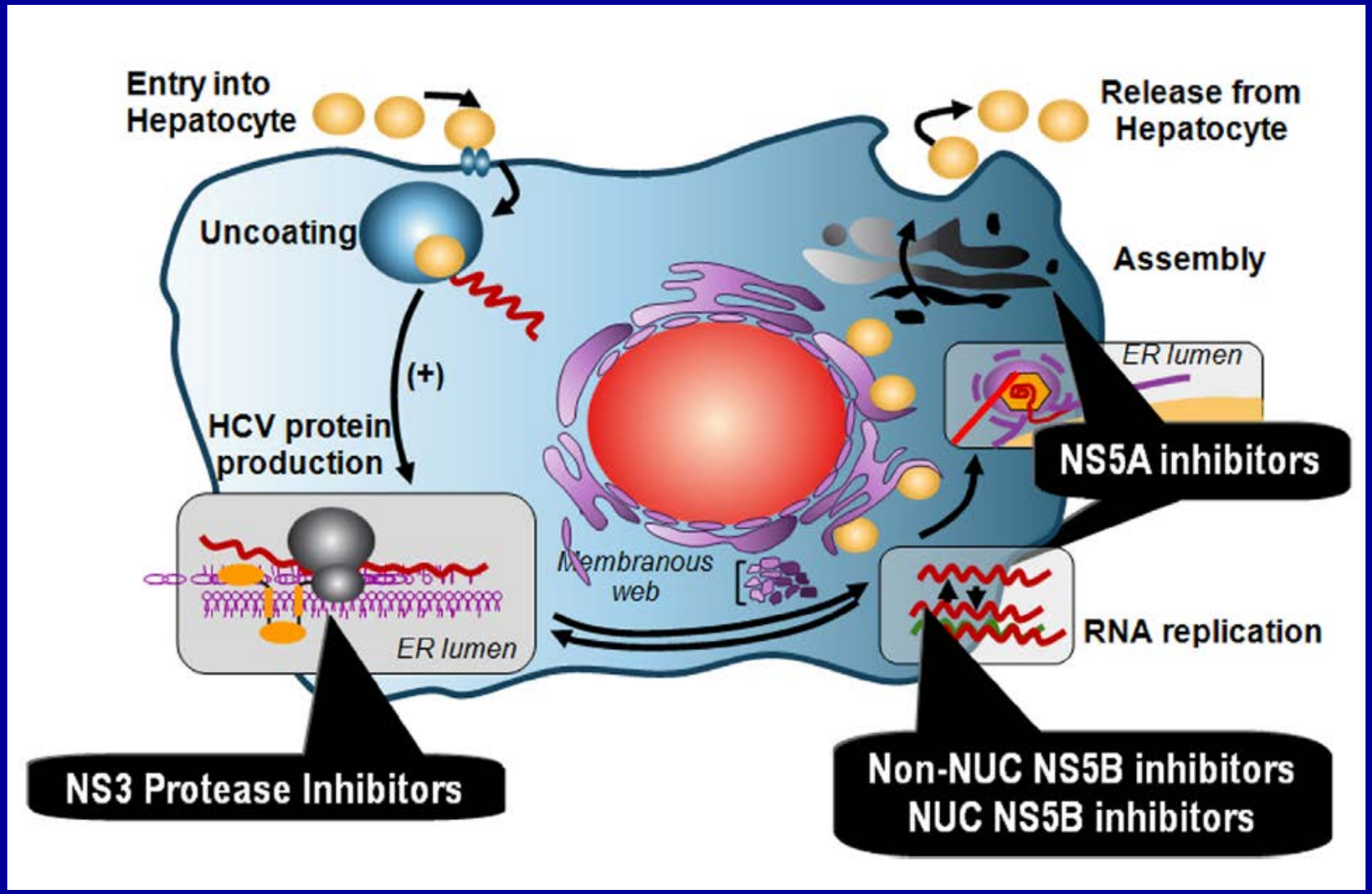
Year of Transplant	Removal for death or too sick			Transplants (deceased + living donors)		
	No HCV diagnosis	HCV diagnosis		No HCV diagnosis	HCV diagnosis	
	N	N	%	N	N	%
2008	1418	995	41.2 %	4062	1644	28.8 %
2009	1435	1042	42.1 %	4118	1630	28.4 %
2010	1549	1160	42.8 %	4148	1583	27.6 %
2011	1603	1298	44.7 %	4279	1527	26.3 %
2012	1735	1261	42.1 %	4268	1463	25.5 %
Total	**7740**	**5756**	**42.6 %**	**20875**	**7847**	**27.3 %**

[a] Model for end-stage liver disease. [b] HCV diagnosis was based upon a listing diagnosis of hepatitis C. [c] The percentage of HCV cases at each MELD score or status was calculated from [(N, HCV diagnosis)/N for each MELD category] x 100 %. [d] The MELD distribution was calculated from [(N, No HCV or HCV diagnosis)/Total N of No HCV or HCV diagnosis, respectively] × 100 %

If he had a living donor, would that influence your decision to treat?

Would you treat pre- or post-LDLT?

How should we treat the cirrhotic patient with HCV GT3 who has failed prior treatment?



Gane EJ, Agarwal K. Am J Transplant 2014;14:994-1002.

What are the "approved" treatment options for HCV GT3?

1. Peginterferon (PEG)
2. PEG + ribavirin (RBV)
3. PEG/RBV + Simiprevir (SMV)
4. PEG/RBV + Sofosbuvir (SOF)
5. SOF + RBV
6. SMV/SOF ± RBV
7. SOF/LDV ± RBV
8. PTV/r/OMB/DAS ± RBV
9. SOF/DAC ± RBV

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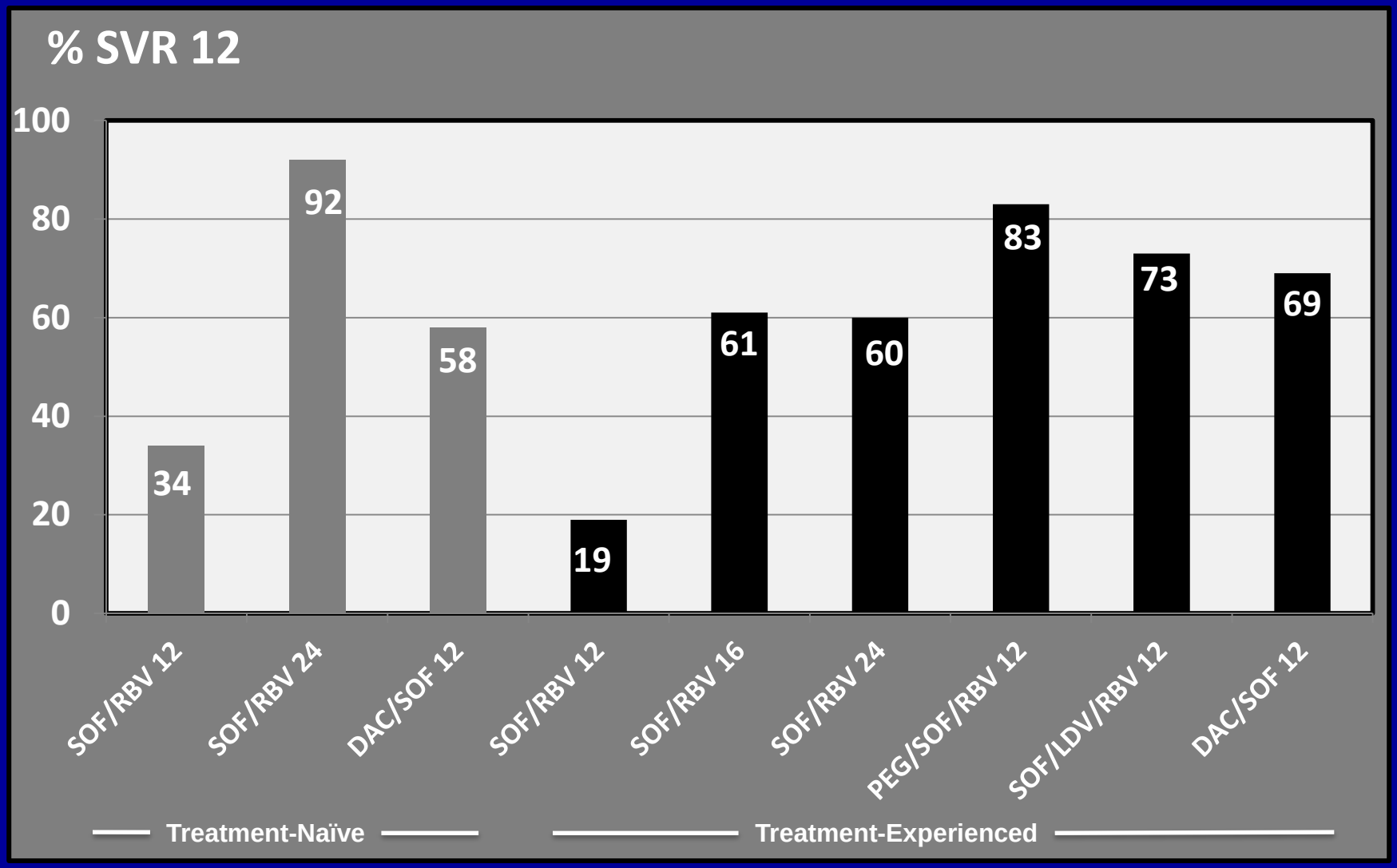
Red – US and EU; Magenta - EU

Rates of SVR in HCV GT3 Cirrhosis



Which of the following treatments do you recommend?

1. Peginterferon (PEG)
2. PEG + ribavirin (RBV)
3. PEG/RBV + Simiprevir (SMV)
4. PEG/RBV + Sofosbuvir (SOF)
5. SOF + RBV
6. SMV/SOF ± RBV
7. SOF/LDV ± RBV
8. PTV/r/OMB/DAS ± RBV
9. SOF/DAC ± RBV

I chose:

1. Peginterferon (PEG)
2. PEG + ribavirin (RBV)
3. PEG/RBV + Simiprevir (SMV)
4. PEG/RBV + Sofosbuvir (SOF)
5. SOF + RBV
6. SMV/SOF ± RBV
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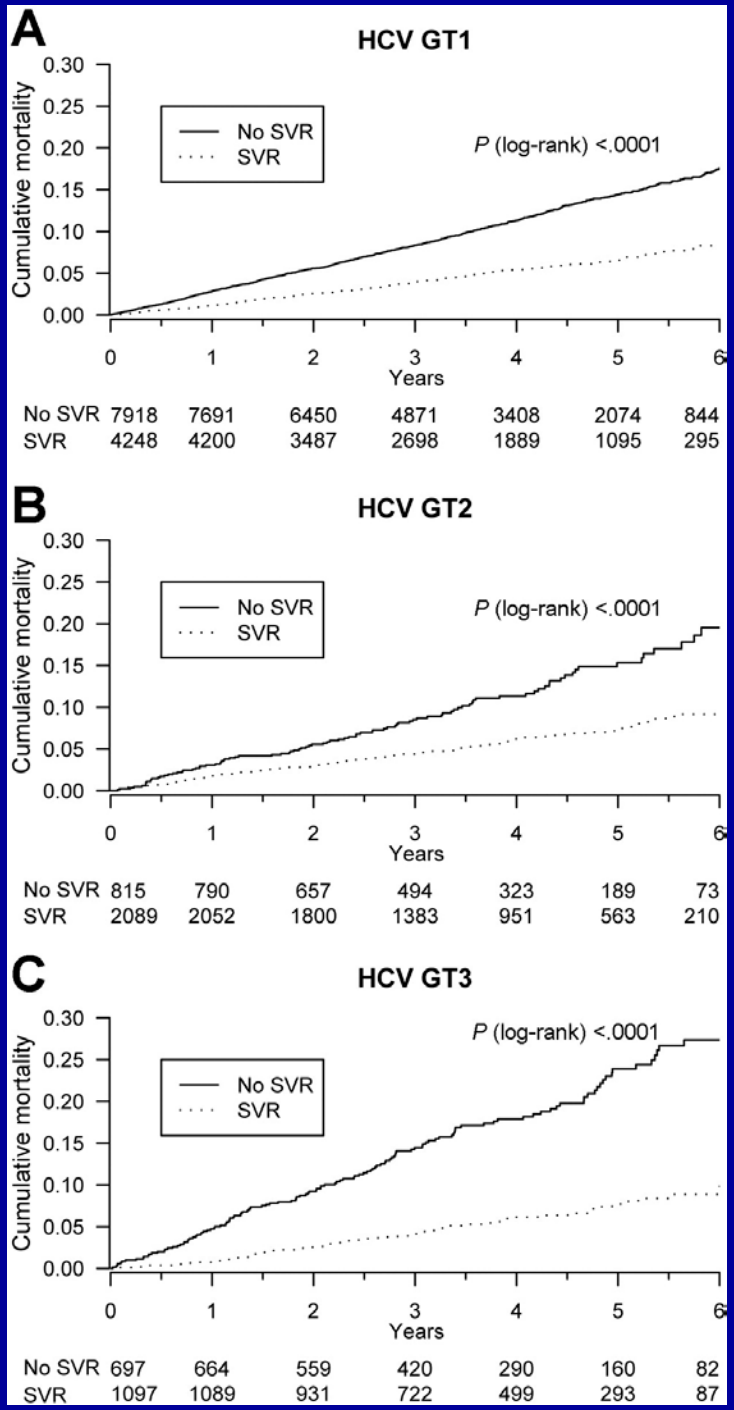
Should patients infected with HCV GT3 be given priority for Rx?



HCV Genotype 3 patients without SVR had the most rapid progression and highest cumulative mortality – conversely, SVR achieved the greatest reduction in mortality in HCV GT3.

Backus L, et al.
Clinical Gastroenterol Hepatol 2011; 9:509-516.

Compared to GTs 1 and 2, GT 3 has:

1. Higher risk for HCC, lower risk for Decomp
2. Lower risk for HCC, higher risk for Decomp
3. Higher risk for HCC and Decomp
4. Lower risk for HCC and Decomp

Compared to GTs 1 and 2, GT 3 has:

1. Higher risk for HCC, lower risk for Decomp
2. Lower risk for HCC, higher risk for Decomp
3. Higher risk for HCC and Decomp
4. Lower risk for HCC and Decomp

Outcome of our Case:

1. SVR 12
2. Cirrhosis stable, MELD 11, Pltl 105K
3. Clinically well

What benefits, if any, did he derive from Rx of HCV?
Is he now in "MELD Purgatory"?
Should we appeal to RRB for more MELD points?
If he has a donor, should we pursue LDLT?