Clinical Pharmacology of HCV Drugs in Severe Liver Disease

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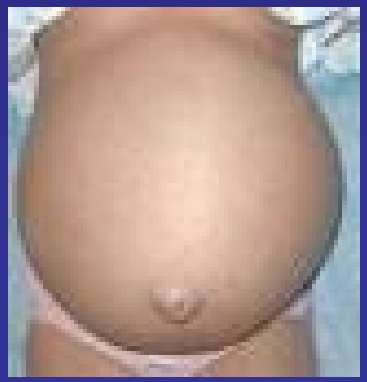
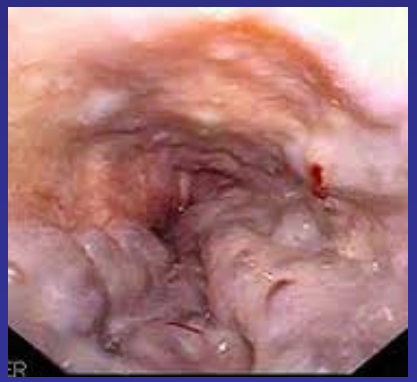
Decompensated Cirrhosis

- Ascites
- Encephalopathy
- Bleeding varices
- Coagulopathy (PT > 3 seconds > control)





Estimates of Hepatic Impairment

Child-Pugh

- Bilirubin
- INR
- Albumin
- Encephalopathy
- Ascites

- *Assigns points then patients categorized*
  - *Child-Pugh A = mild*
  - *Child-Pugh B = moderate*
  - *Child-Pugh C = severe*

MELD

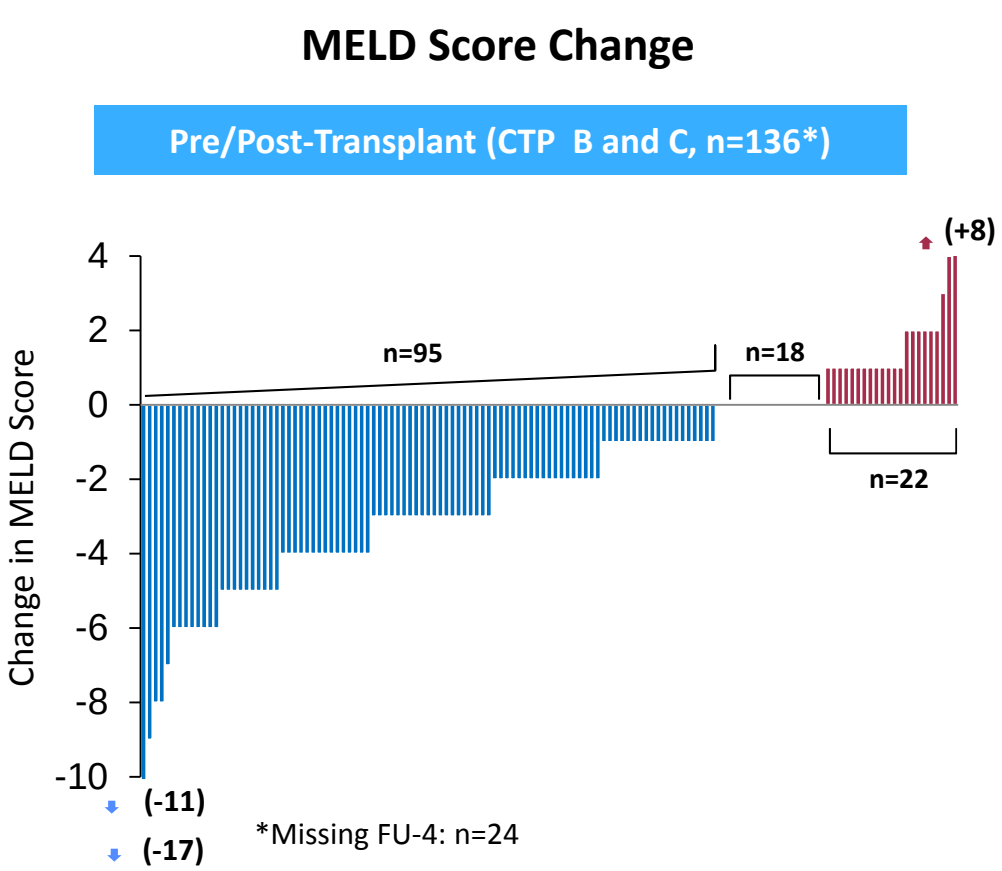
- Creatinine
- Bilirubin
- INR

- *Higher MELD = Higher risk of 3 month mortality and greater prioritization for liver transplantation*

True or False?

- Treating HCV in a patient with decompensated cirrhosis is in their best interests.

MELD Scores Improve

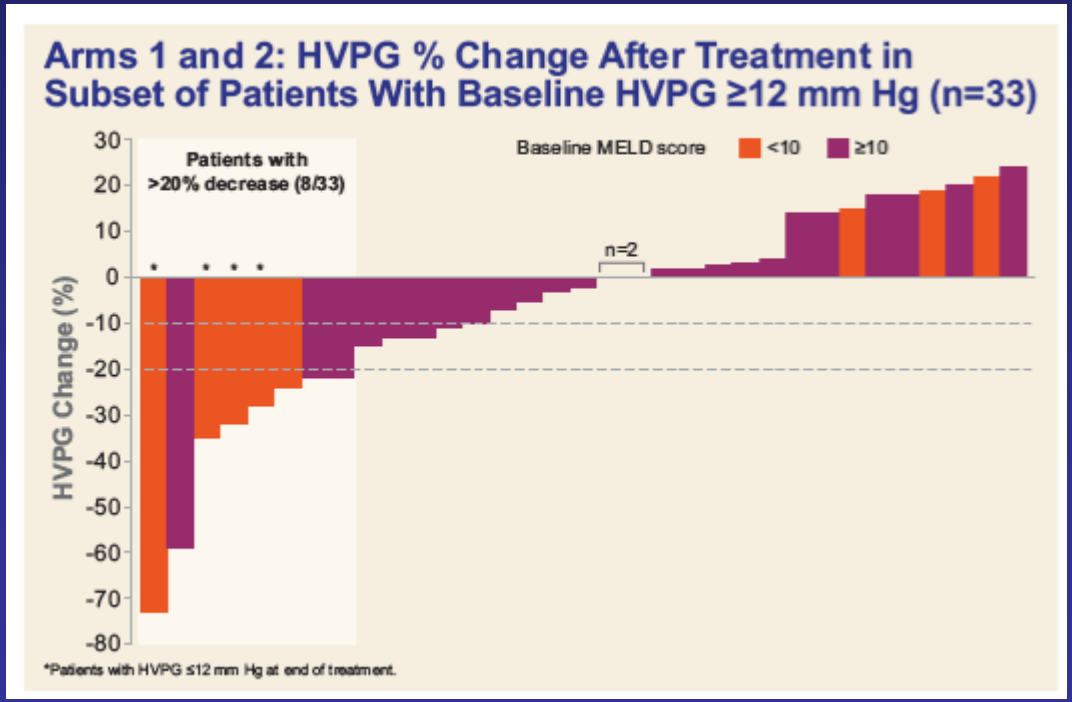


- Primarily due to improvements in bilirubin and albumin
- Anecdotally, although patients achieve SVR, some do not feel better

SOLAR-2, SOF/LDV/RBV x 12 or 24 weeks, Manns M, EASL 2015, G02

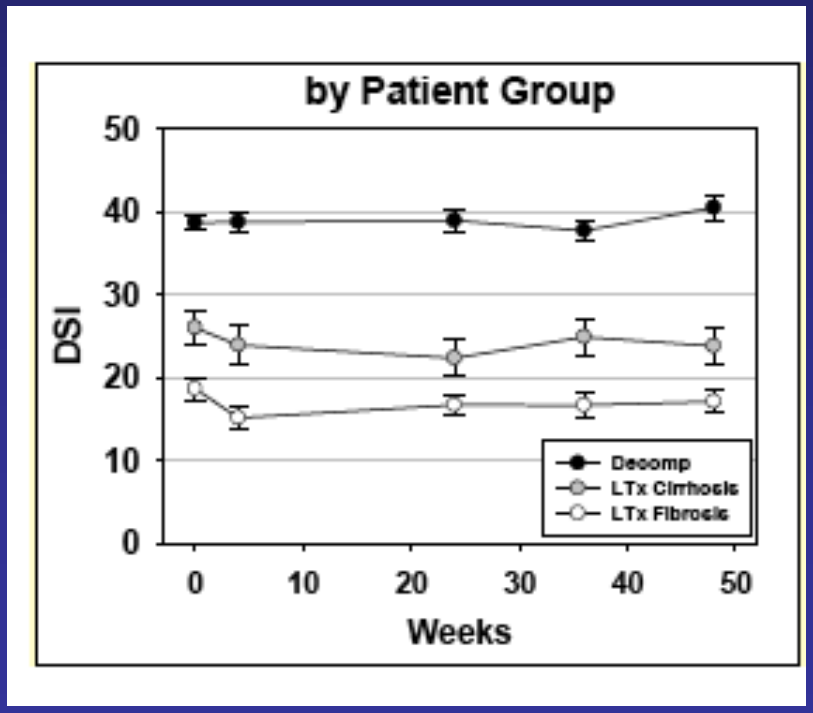
But portal hypertension/shunting does not appear to improve

With SOF/RBV treatment for 48 weeks, very few with a baseline MELD >10 had a significant on-treatment improvement in HVPG



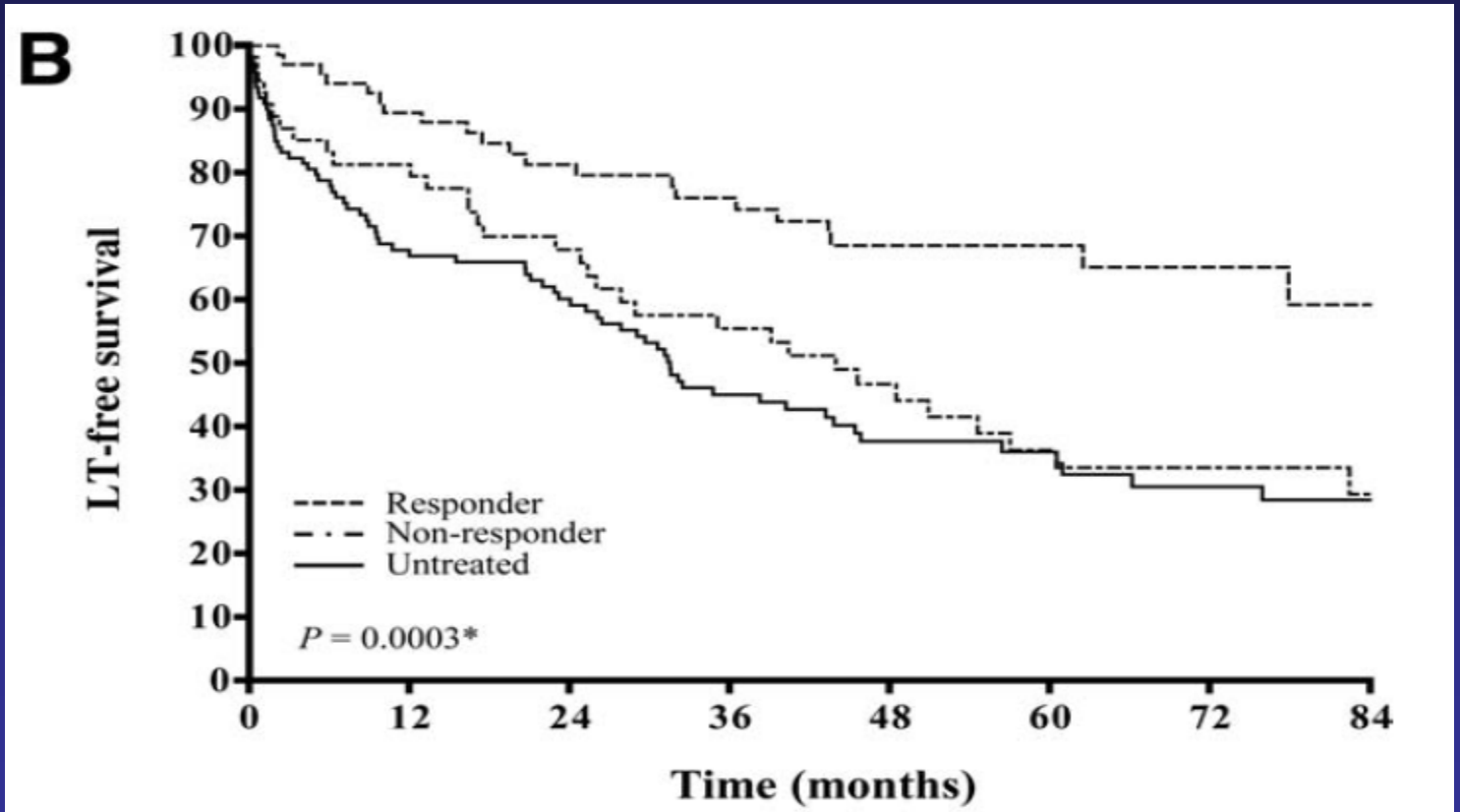
Afdhal N, et al. EASL 2015

10 patients with decompensated cirrhosis, no improvement in portal systemic shunting during or 24-36 weeks after SOF/LDV/RBV treatment



Burton JR, Jr. et al. EASL 2015

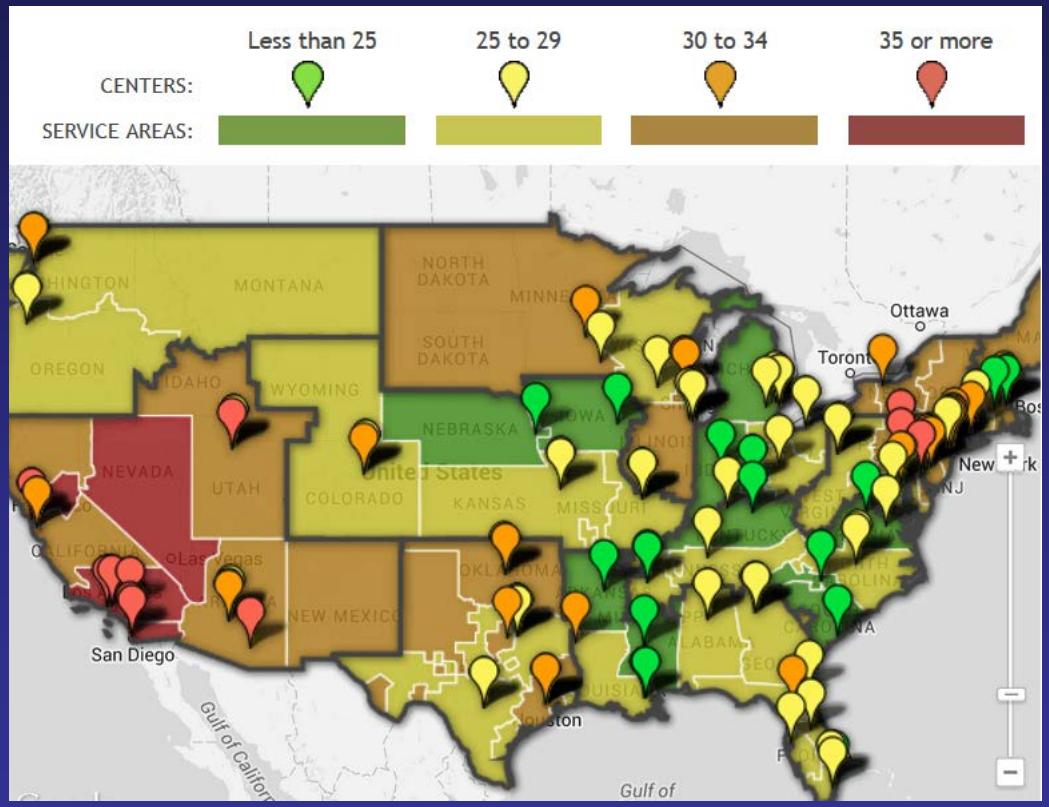
Survival Improved with Suppression of HBV



Responder	72	59	50	43	32	22	17	9
Non-responder	55	44	34	27	21	14	12	8
Untreated	127	73	62	41	28	21	16	14

Jang JW, et al. Hepatology 2015;61:1809-1820

Willingness to Treat May Depend on Geography



Transplant Center	#tx	#waiting	Average MELD
UCSF	157	772	35
UnivMD	115	425	33
UCLA	168	383	37
Mt Sinai	107	332	32
UColo	70	572	29
Baylor	91	279	29
Georgetown	102	223	25
Jackson	122	153	25
Emory	154	122	25
Vanderbilt	152	160	25
UNMC	94	137	22
Indiana	141	67	22
MUSC	72	50	24
Ochsner, Louisiana	196	111	23

Source: http://host.madison.com/app/interactive/transplant-maps/index-liver.html, median MELD data 6/13-7/14, waitlist 5/1/15, Source Organ Procurement and Transplantation Network, Scientific Registry of Transplant Recipients

Pharmacologic Considerations

1. What are the pathophysiologic consequences of decompensated cirrhosis?
   - How does this influence DAA selection and dosing in this population?

2. Magnitude of interactions in individuals with decompensated cirrhosis?

Features of Advanced Liver Disease which may Alter DAA PK

1. Hepatic enzyme expression and/or function
2. Membrane transporter expression and/or function
3. Protein Binding
4. Portal-Systemic Shunting
5. Phosphorylation enzyme expression and/or function
6. Renal Impairment
7. Reduced gastrointestinal absorption

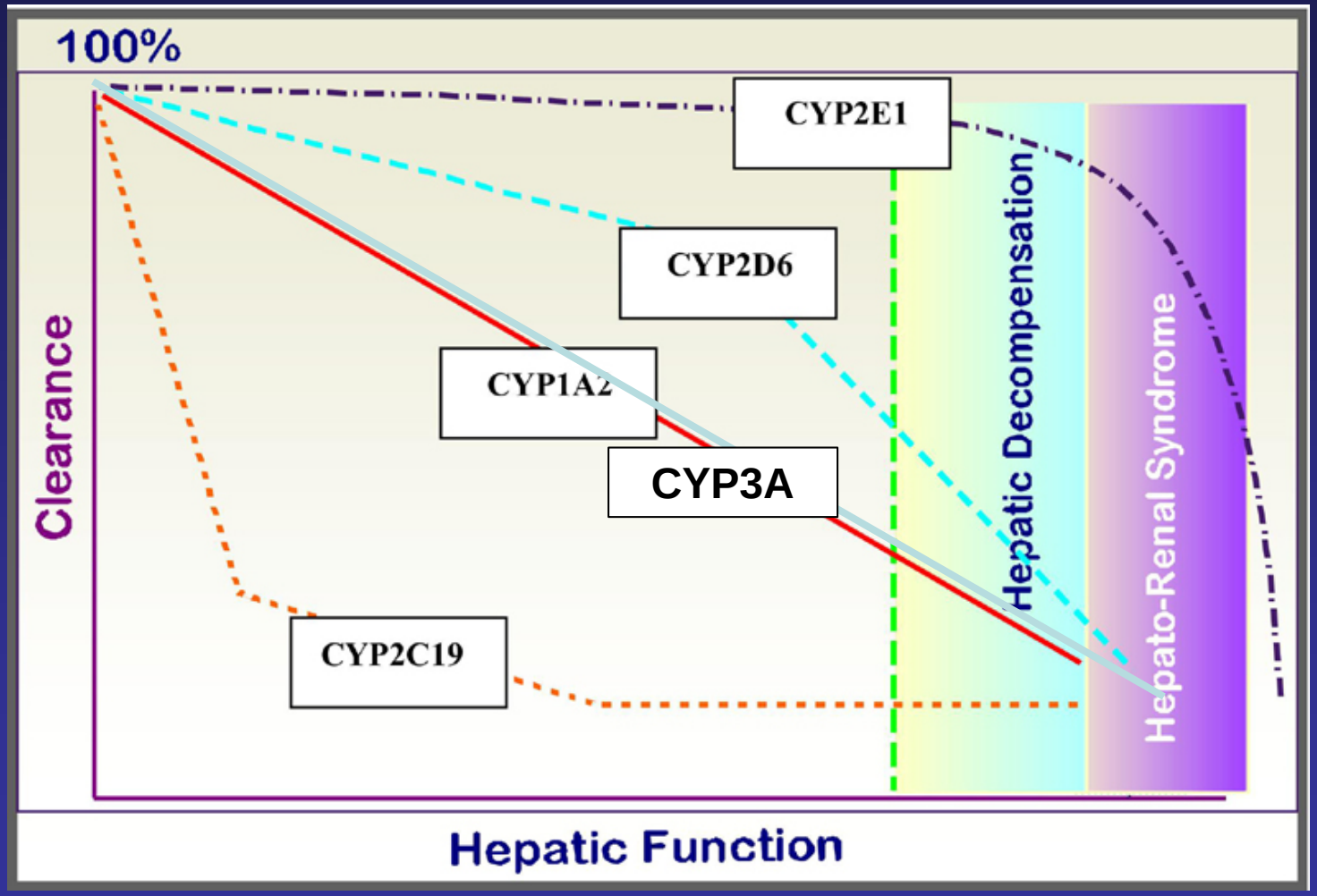
1. Hepatic Enzyme Expression and Function

- Phase I metabolism (e.g., oxidation) affected earlier in disease severity
  - e.g., cytochrome P450 (CYP) enzymes
  - BUT declines are isoform-specific

- Phase II metabolism affected later in disease severity
  - e.g., glucuronidation, sulfation, acetylation, methylation, glutathione conjugation, amino acid conjugation

Verbeeck RK. Eur J Clin Pharmcol 2008;64:1147-1161

CYP Enzyme Expression and Function with Progressive Hepatic Impairment



Modified from figure by Branch RA, CPT 1998;64:462

2. Transporter Expression in Liver Disease

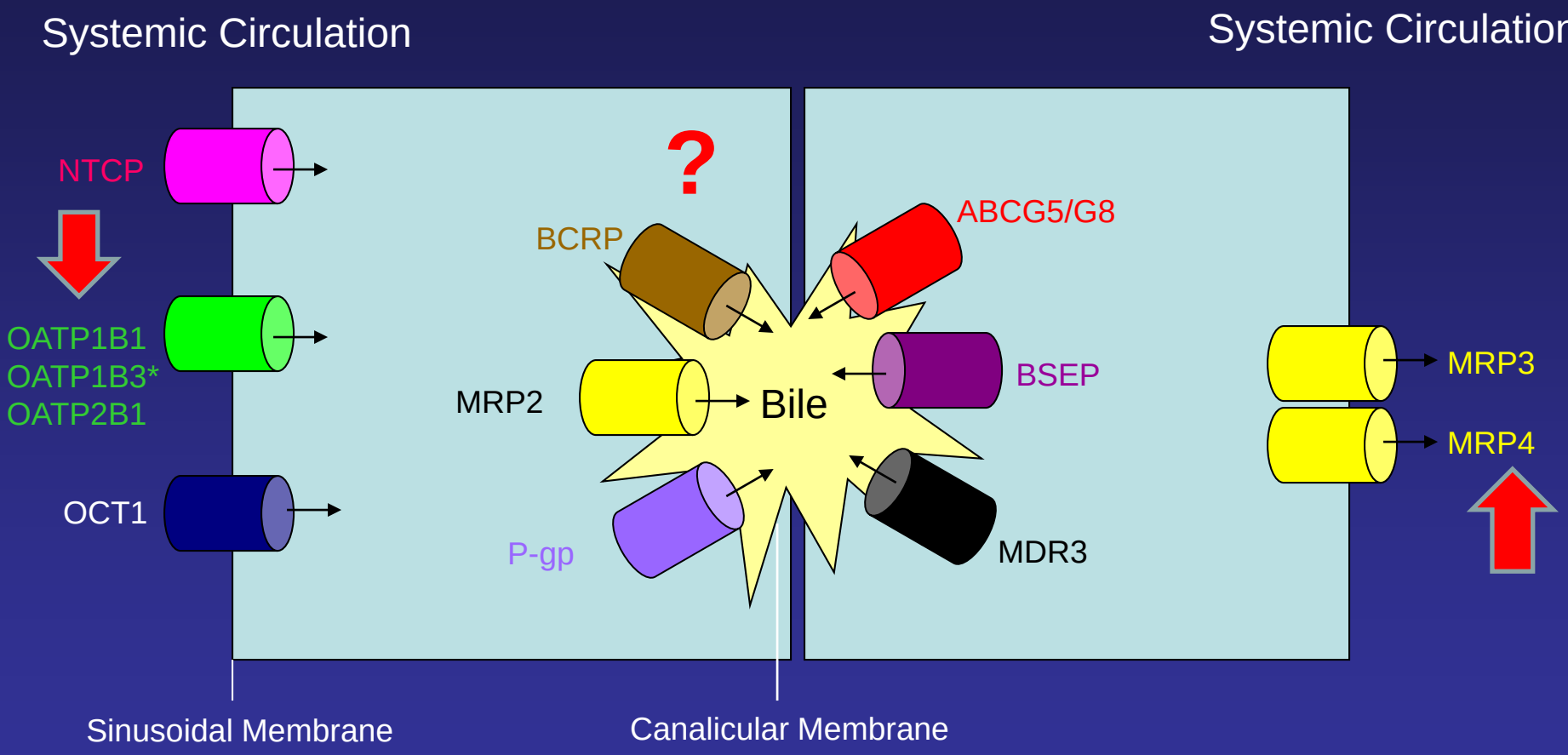


Figure adapted from Oswald S. et al. Xenobiotica 2007;37(10-11):1171, [1]Nakai K, et al. Drug Metab & Dispos 2008;36(9):1786,[2]Ogasawara K, et al. Drug Metabol PK 2010;25(2):190, [3]Bonin S, et al. Mol Med 2002;8(6):318.

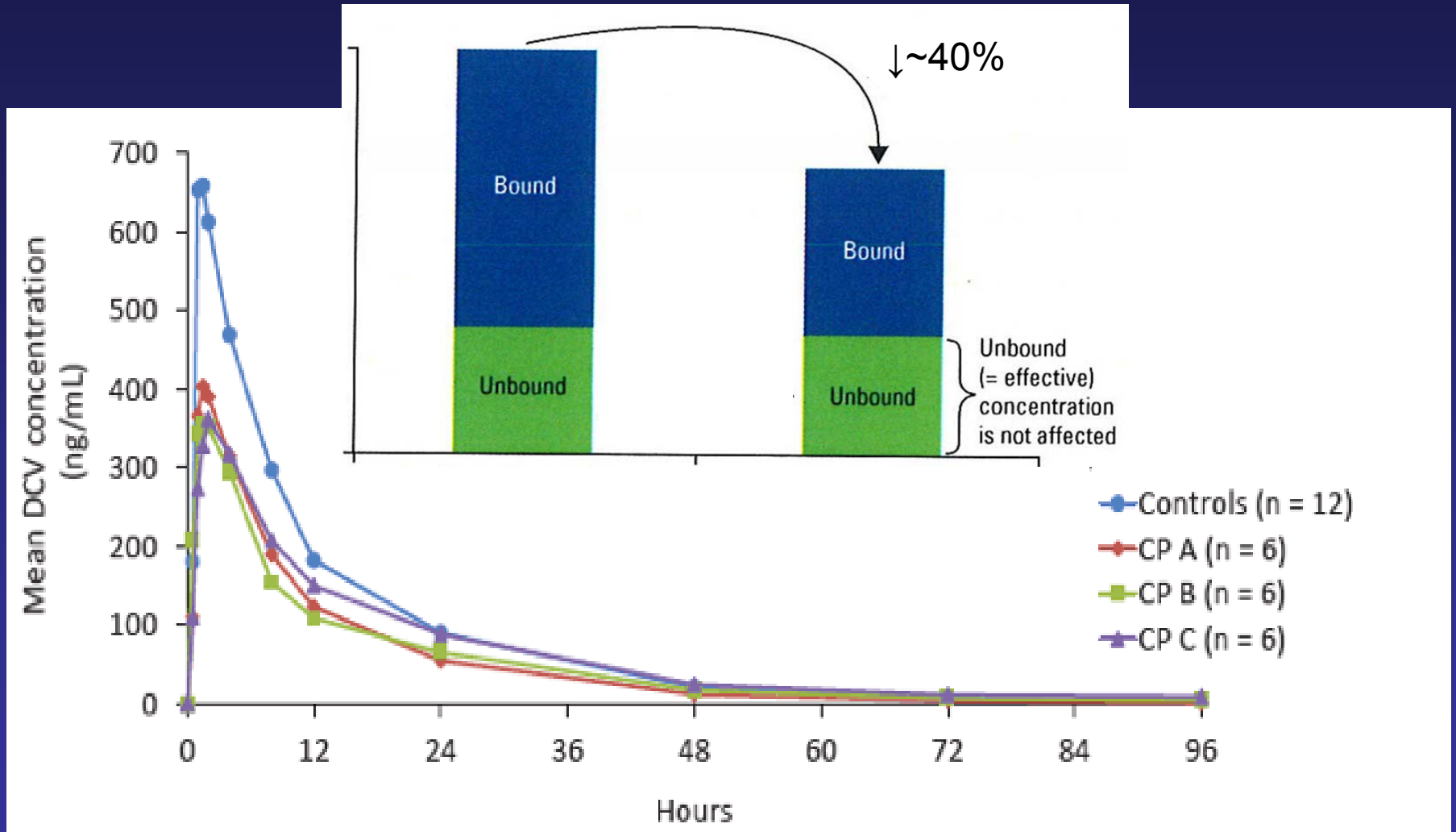
3. Protein Binding

- Impaired production of plasma proteins results in decreased plasma binding of several drugs.
  - May also be a contribution of competition for binding sites with endogenous substances
  - Perhaps a reduction in the quality of protein

- For highly protein bound drugs (>90%), even small changes in binding can have large effects on drug PK.

Verbeeck RK. Eur J Clin Pharmcol 2008;64:1147-1161

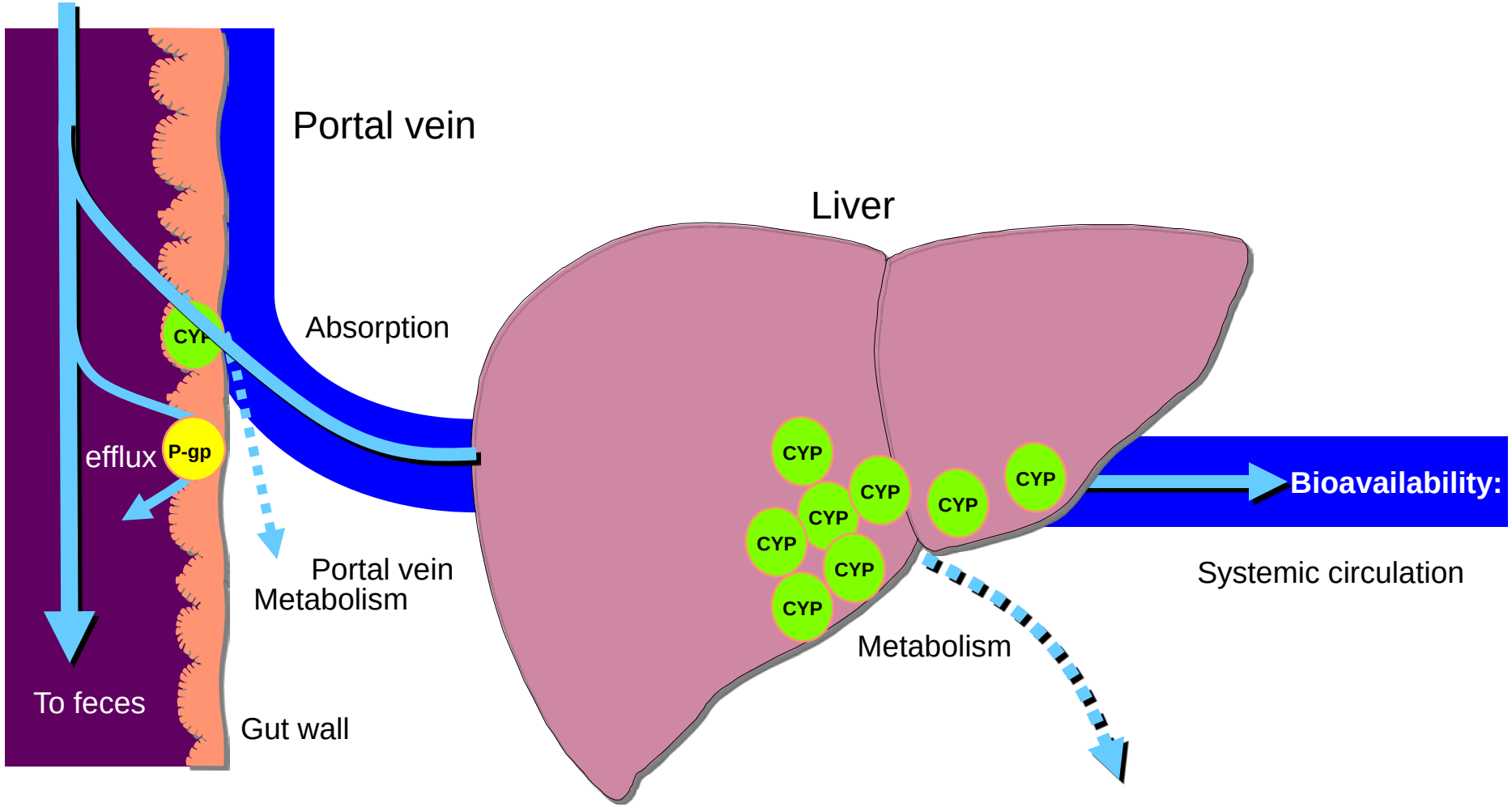
Daclatasvir Unbound Concentrations Unchanged in Hepatic Impairment



Total concentrations appear lower, but free amount is unchanged.

Bifano, M. 62nd AASLD 2011

4. Portal-Systemic Shunting



Fraction extracted and metabolized (E_H)

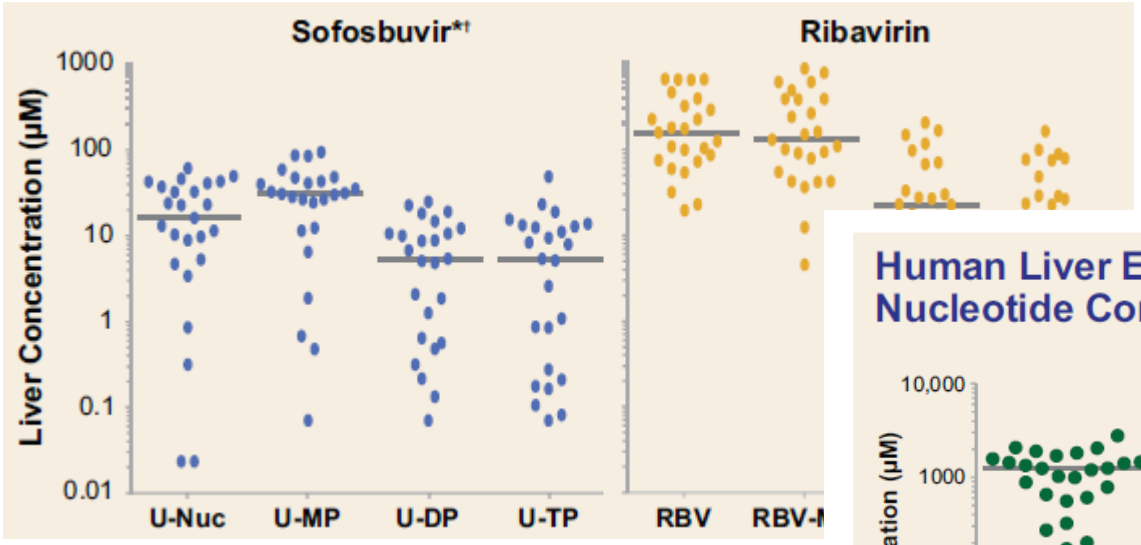
Portal-Systemic Shunting Effects on Drug Pharmacokinetics

Increased bioavailability and thus plasma exposures due to shunting

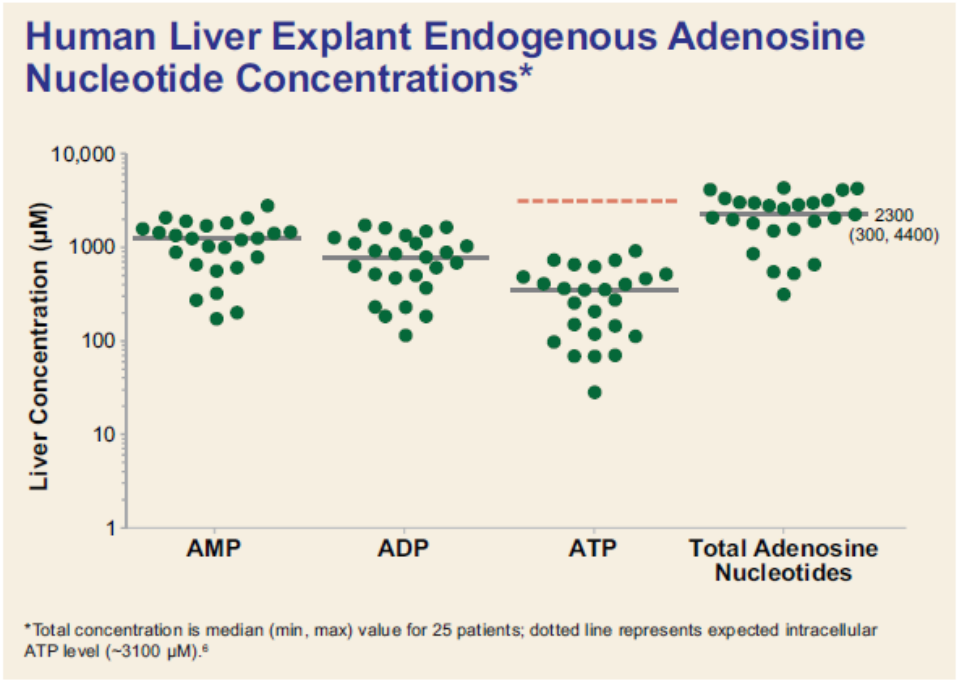
Drug	Normal	Cirrhosis	Fold increase
Carvedilol	0.19	0.83	4.4
Chlormethiazole	0.10	1.16	11.6
Labetalol	0.33	0.63	1.9
Meperidine	0.48	0.87	1.8
Metoprolol	0.50	0.84	1.7
Midazolam	0.38	0.76	2.0
Morphine	0.47	1.01	2.1
Nifedipine	0.51	0.91	1.8
Nisoldipine	0.04	0.15	3.8
Pentazocine	0.18	0.68	3.8
Propranolol	0.36	0.60	1.7
Verapamil	0.10	0.16	1.6

Verbeeck RK. Eur J Clin Pharmcol 2008;64:1147-1161

5. Alterations in Phosphorylation Enzyme Expression or Function?



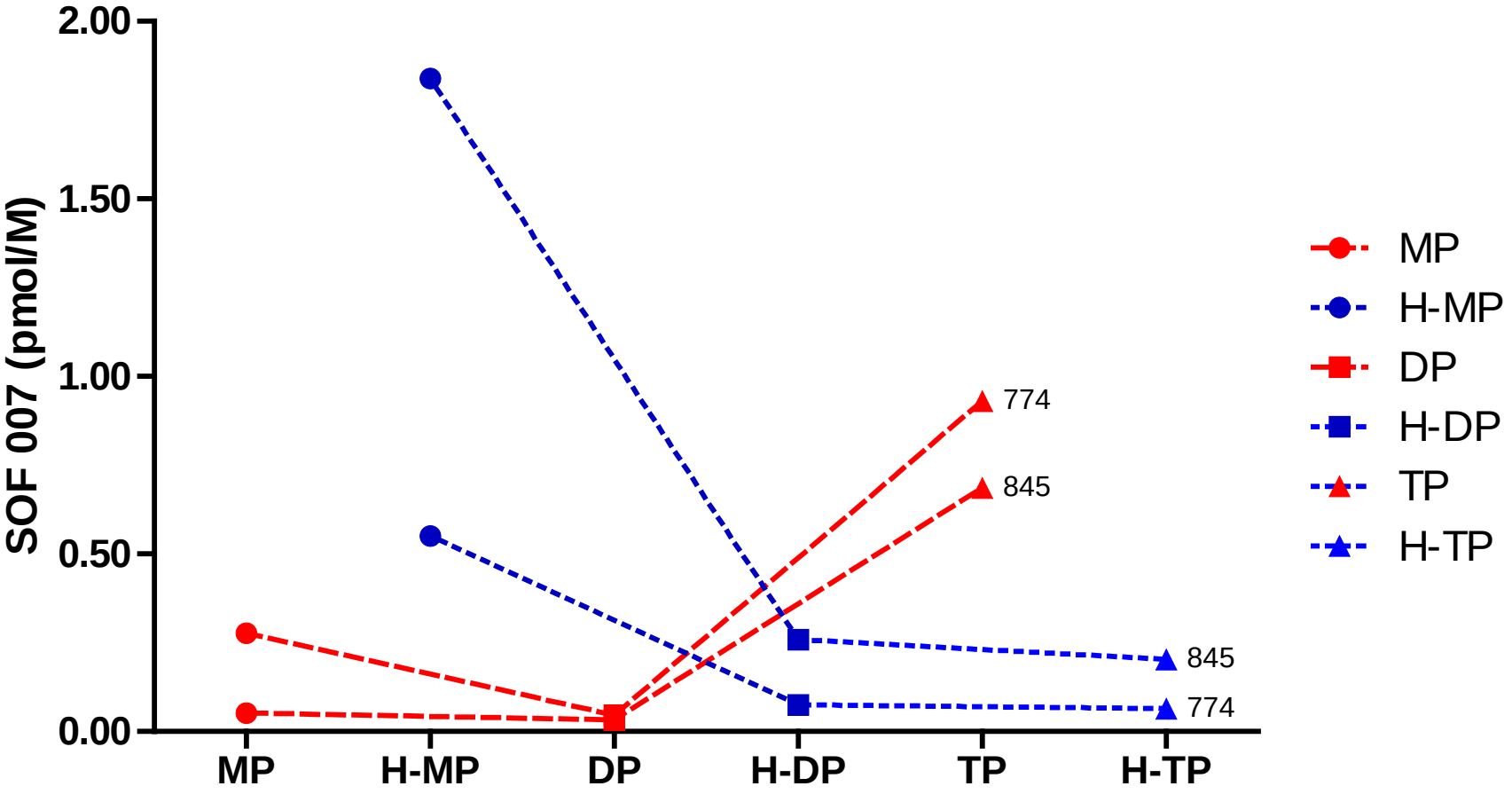
Liver tissue flash frozen



- Absolute ATP and ratio of ATP to AMP and ADP lower than historical data
- Evidence of dephosphorylation of nucleotides with sample processing
- Comparator based on healthy individuals without liver disease, also not on RBV

Babusis D, Ray AS. AASLD 2013, #1091

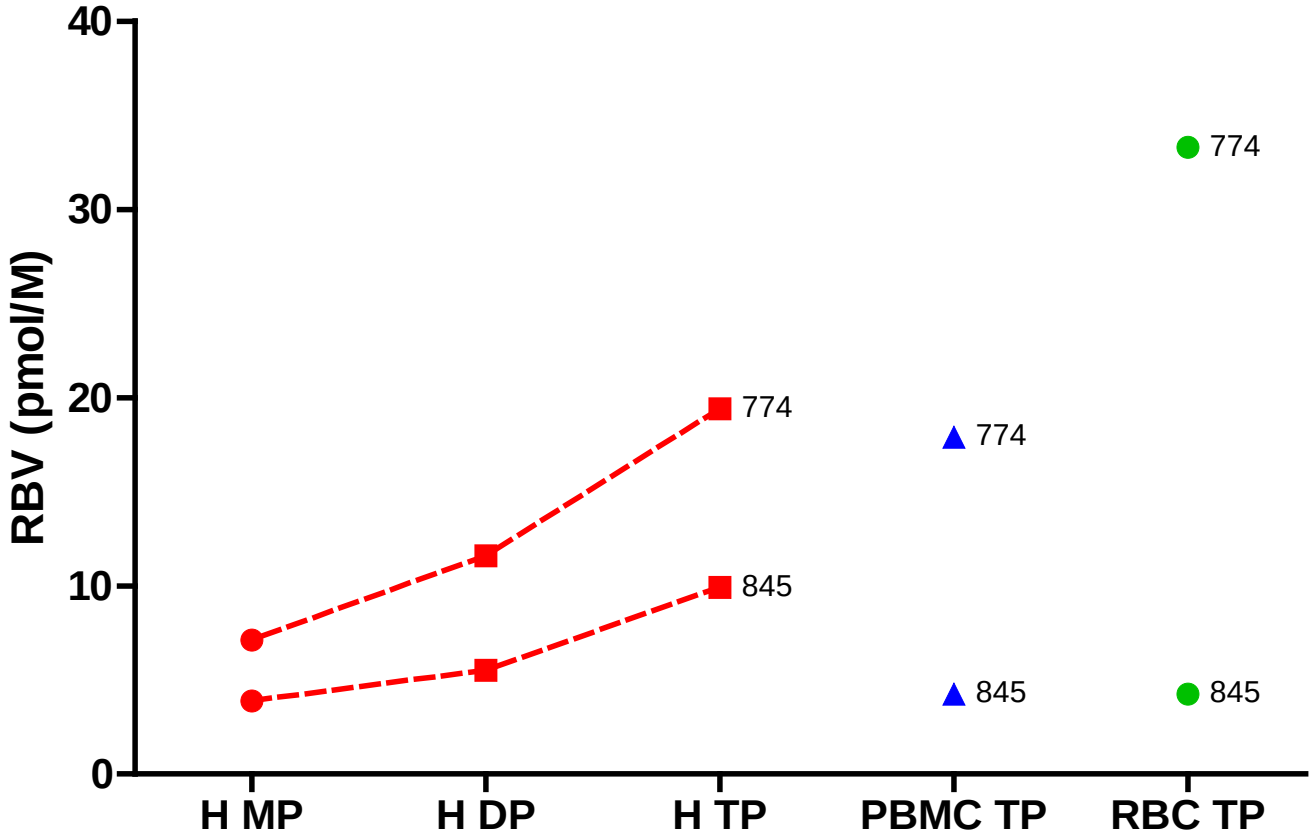
5. 007 MP, DP, TP in paired PBMCs (red) vs. hepatocytes (blue)



007-TP levels are ~4x higher than 007-MP in PBMC[1]

[1]Rower JE, CROI 2015, Rower JE, unpublished data

RBV-TP was still predominant anabolite in hepatocytes



RBV-TP levels are ~3.5x higher than RBV-MP in PBMC[1]

[1]Wu L, D'Argenio DZ, Kiser JJ, et al. AAC 2015; Rower JE, Kiser JJ, unpublished data

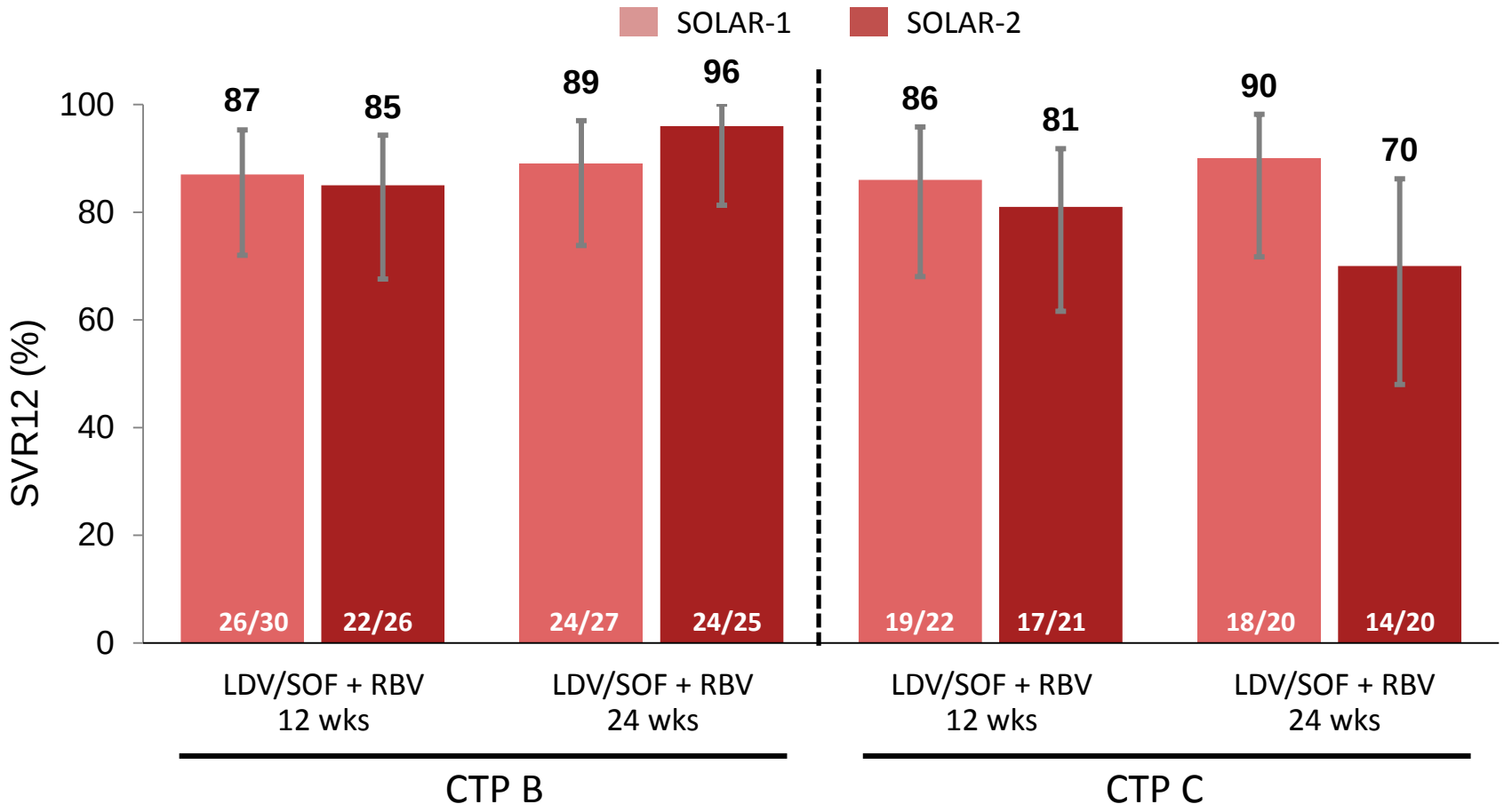
DAA Plasma PK in Decompensated Cirrhosis

Fold change in hepatic impairment vs. controls

DAA	Class	Child Pugh B	Child Pugh C
Sofosbuvir[1]	NI	↑ 2.3-fold	↑ 2.5-fold
GS-331007[1]		↔	↔
Daclatasvir[2]	NS5A	↓ 38%	↓ 36%
Ledipasvir[3]	NS5A	↔	↔
Ombitasvir[4]	NS5A	↓ 30%	↓ 55%
Elbasvir[5]	NS5A	↓ 28%	No data
Grazoprevir[6]	PI	↑ 4.88-fold	No data
Paritaprevir[4]	PI	↑ 1.62-fold	↑ 10.23-fold
Simeprevir[7]	PI	↑ 2.4-fold	↑ 5-fold
Dasabuvir[4]	NNI	↓ 16%	↑ 4-fold

[1]Lawitz E, et al. EASL 2012, [2]Bifano M, et al. 62nd AASLD 2011, [3]German P, et al. 64th AASLD 2013, [4]Khatri A, [5]Marshall WL, et al. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy 2014, [6]Caro L, et al. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy 2014, [7]Ouwerkerk-Mahadaven S, et al. EASL 2013

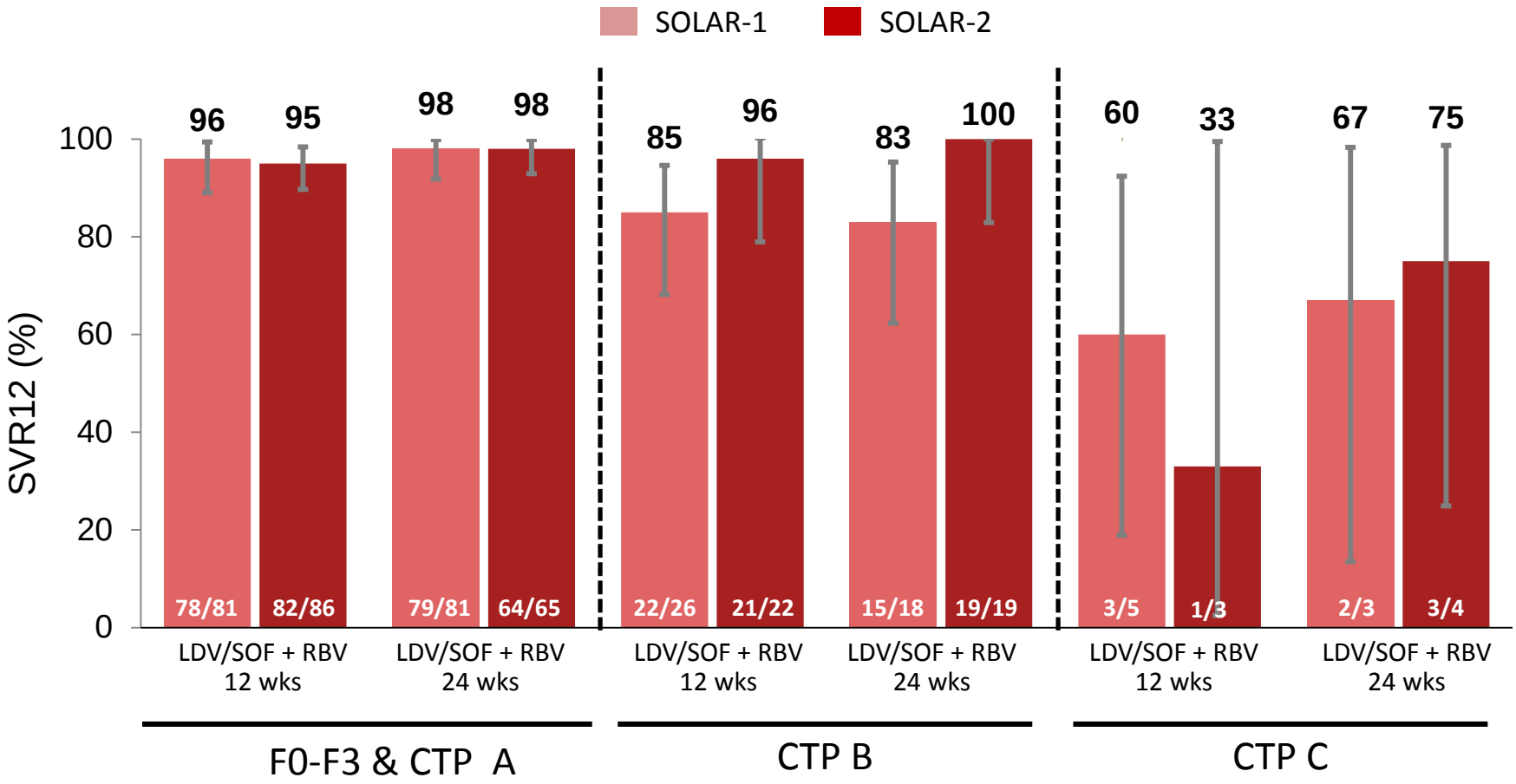
SOF (NS5B), LDV (NS5A) + RBV in Decompensated Cirrhotics: Pre-Transplant



The SVR12 analysis included all subjects except those who had undergone transplantation prior to SVR12 at last visit prior to transplantation. Error bars represent 90% confidence intervals.

SOLAR-1 and SOLAR-2, Reddy, AASLD, 2014, Oral #8; Manns, EASL, 2015, GO2

SOF (NS5B), LDV (NS5A) + RBV in Decompensated Cirrhotics: Post-Transplant



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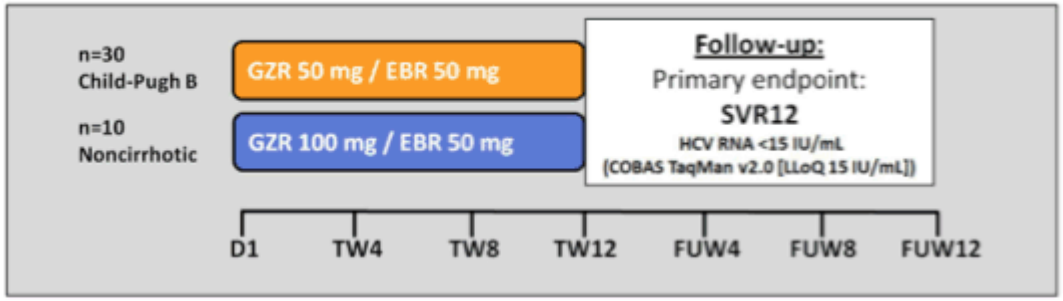
SOLAR-1 and SOLAR-2, Reddy, AASLD, 2014, Oral #8; Manns, EASL, 2015, GO2

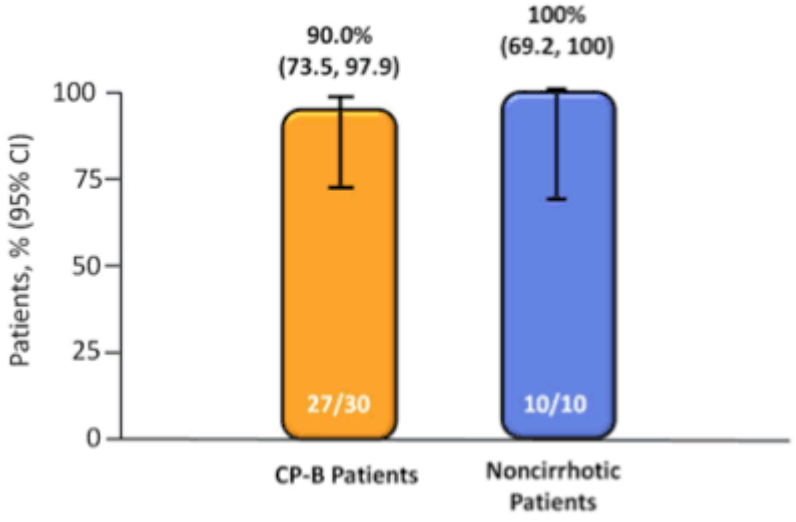
Grazoprevir (PI) + Elbasvir (NS5A) in Moderate Hepatic Impairment



- Phase 2, nonrandomized, open-label study
- 30 patients with HCV G1 infection and CP-B cirrhosis
- 10 noncirrhotic patients with HCV G1 infection were enrolled for PK analyses

Grazoprevir dose was halved to account for the interaction observed in HCV seronegative individuals with moderate impairment

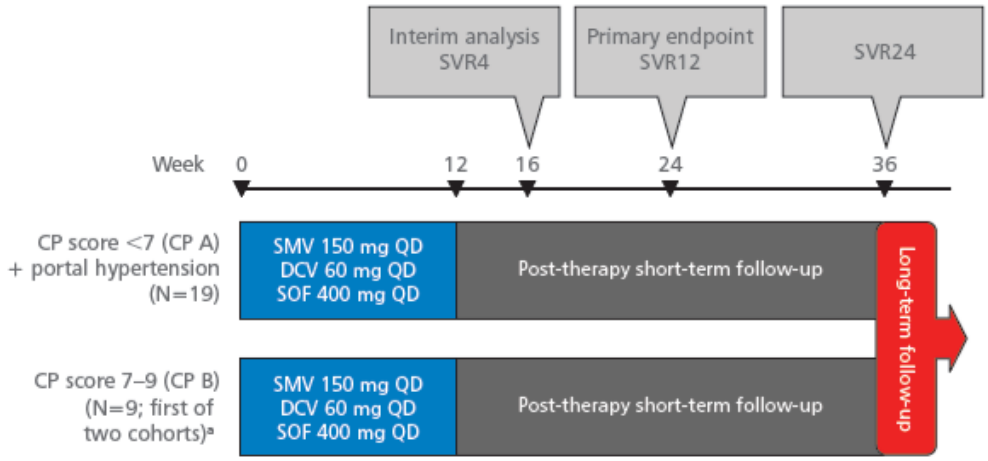
Additional studies are needed, but now there is precedent for adjusting the PI dose to accommodate PK alterations in decompensated cirrhosis with a high rate of SVR.



C-SALT, Jacobson I, EASL 2015

Simeprevir (PI), Daclatasvir (NS5A), + Sofosbuvir (NS5B)

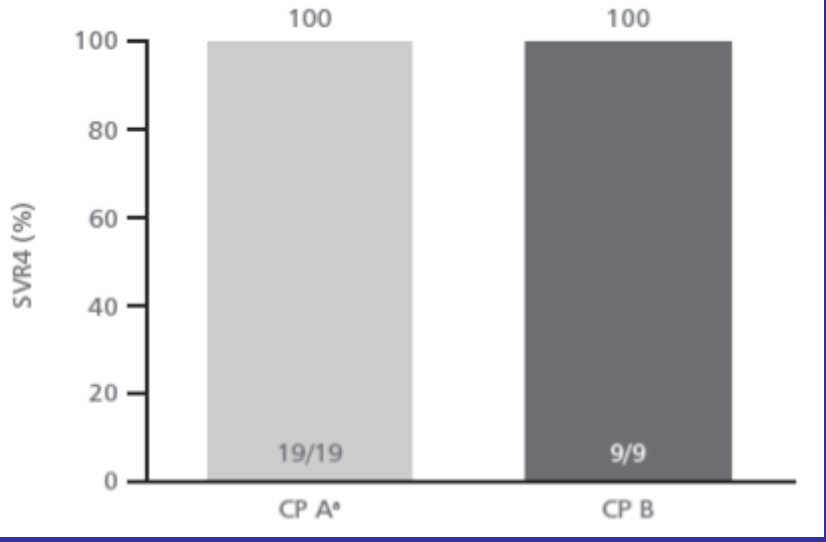
Figure 1: IMPACT study design.



HCV RNA was measured using the Roche COBAS® Ampliprep/COBAS TaqMan® HCV assay version 2.0 (lower limit of quantification = limit of detection = 15 IU/mL).
[a]The CP B group was split into two cohorts. This interim analysis included the first cohort (n=9) in order to assess s and pharmacokinetic (PK) parameters in CP B patients prior to enrolling the remaining patients in this group.
CP, Child-Pugh; DCV, daclatasvir; HCV, hepatitis C virus; QD, once daily; SMV, simeprevir; SOF, sofosbuvir; SVR, sustai virologic response 4 (SVR4), 12 (SVR12) or 24 (SVR24) weeks after actual end of treatment.

9/9 with Child Pugh B achieved SVR4

Simeprevir exposures were 1.8-fold higher in CP B vs. A



IMPACT, Lawitz E, et al. EASL 2015

Pharmacologic Considerations

1. What are the pathophysiologic consequences of decompensated cirrhosis?
   - How does this influence DAA selection and dosing in this population?

2. Magnitude of interactions in individuals with decompensated cirrhosis?

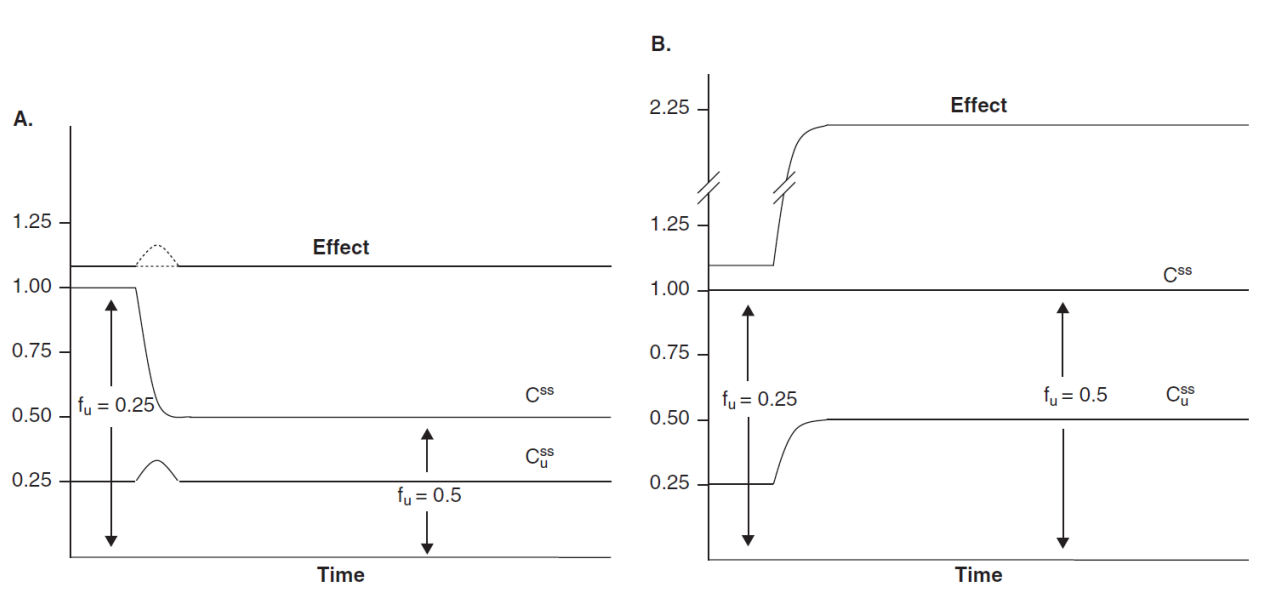
Example of the Magnitude of Inhibition Interaction in ESLD

- With reversible CYP1A2 inhibitor, fluvoxamine and CYP1A2 substrate, lidocaine
- The effect is LESS in decompensated cirrhosis vs. those without hepatic impairment

	% of Lidocaine CL Inhibition by Fluvoxamine
Healthy	60%
Child Pugh A	44%
Child Pugh C	9%

Palatini P, Orlando R, De Martin S. Expert Opin Drug Metab Toxicol 2010;6(10):1215-1230

Need to measure free levels of drug in decompensated cirrhosis



- Total levels artificially lowered
- Protein binding displacement doesn't have clinical relevance in this scenario when CYP metabolism is not inhibited

- Total levels unchanged, but unbound levels and thus pharmacodynamic effects increased
- Protein binding displacement does have important clinical relevance when CYP metabolism is inhibited

Palatini P, Orlando R, De Martin S. Expert Opin Drug Metab Toxicol 2010;6(10):1215-1230

Conclusions and Future Directions

- Viable options for treating patients with decompensated cirrhosis.

- NS5A and NS5B nucleotide polymerase inhibitors possess the pharmacologic properties desirable for the treatment of this population.

Conclusions and Future Directions

- Strategies to determine how best to use other classes (e.g., PIs, NNIs in this population) are desirable.
- Comprehensive studies of the magnitude of drug-drug interactions with DAA (including metabolic, protein binding, and transporter-mediated interactions) in decompensated cirrhotics vs. individuals without hepatic impairment are needed.