TREATMENT OF HCV DECOMPENSATED CIRRHOSIS

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ML SHIFFMAN
DISCLOSURE OF CONFLICTS

Company	Roles	Company	Roles
Abbvie	Advisor, Grant, Speaker	Gilead	Advisor, Grant, Speaker
Bayer	Advisor, Speaker	Intercept	Advisor, Grant, Speaker
Bristol Myers-Squibb	Advisor, Grant, Speaker	Immuron	Grant
Conatus	Grant	Merck	Grant, Advisor, Speaker
CymaBay	Grant	NGMBio	Grant
Daiichi Sankyo	Speaker	Novartis	Grant
Dova	Advisor, Speaker	Optum Rx	Consulting
Exalenz	Grant	Salix	Advisor, Speaker
Galectin	Grant	Shire	Grant
Genfit	Grant	Shionogi	Advisor,

HCV DECOMPENSATED CIRRHOSIS CASE

- 2001:
  - Chronic HCV diagnosed age 54 years
  - Risk: Blood transfusion following MVA age 16 years
  - LBX in 2001: Stage 2 fibrosis, platelet count 175,000
  - HCV genotype 1A, HCV RNA Log 6.2 IU
  - PEGINF-2a 180 mcg QW, Ribavirin 1200 mg QD
- 2016 (Now age 69 years):
  - Severe ascites
  - Variceal bleeding treated with band ligation
  - Developed edema, ascites, HE
  - Paracentesis. Step 1 diuretics.
  - Lactulose BID

(New agenda: Treatment stopped at week 12

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HCV DECOMPENSATED CIRRHOSIS CASE

- Two weeks after hospital discharge:
  - No obvious ascites/edema, grade 1 HE
  - TBILI 2.5 mg/dl (42 umol/L), ALB 3.3 g/dL (33 g/L)
  - NA 136, Scr 1.2 mg/dl (106 umol/L), NH3 60 umol/L
  - HB 10 g/dl (100 g/L), PLT 85,000, INR 1.5
  - AFP 5.7 ng/ml, AFP-L3 12%
  - Ultrasound. Cirrhosis, no mass, patent PV, mild ascites
  - CTP 9, Child Class B, MELD 17

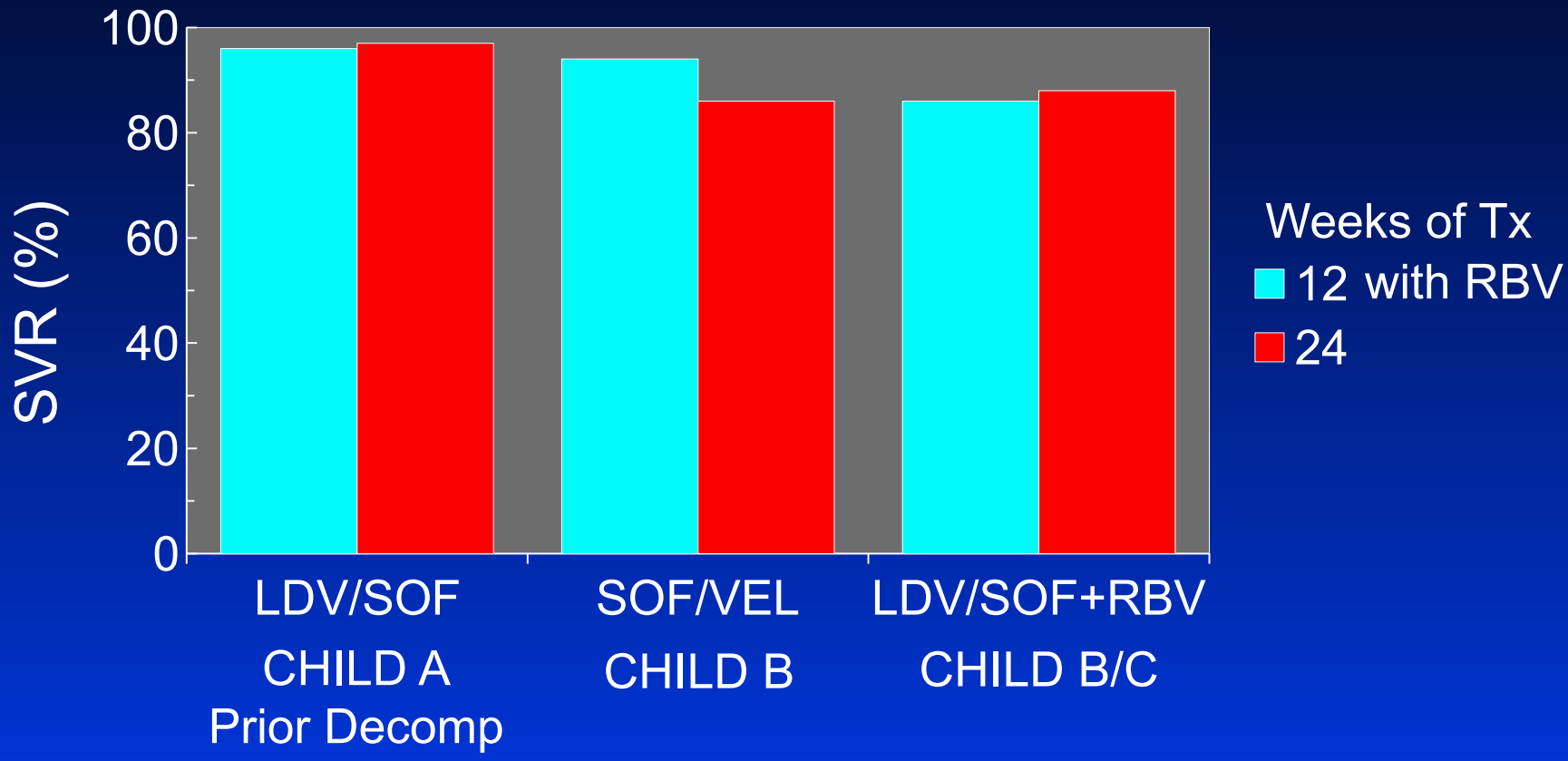
HCV DECOMPENSATED CIRRHOSIS OPTIONS

	Treat HCV	Liver Transplant
Pros	Cure HCV • Improve liver function • Reduce risk of HCC • Avoid transplantation	Eliminate cirrhosis Eliminate risk of HCC Higher HCV cure after LT
Cons	Lower cure rate Risk of HCC persists Symptoms of cirrhosis	Prior to transplant: • Disease progression • Risk of decompensation • Risk of HCC • Risk of never getting a LT Post-LT: • Immune suppression • Other post-LT complications

HCV DECOMPENSATED CIRRHOSIS TREATMENT ISSUES

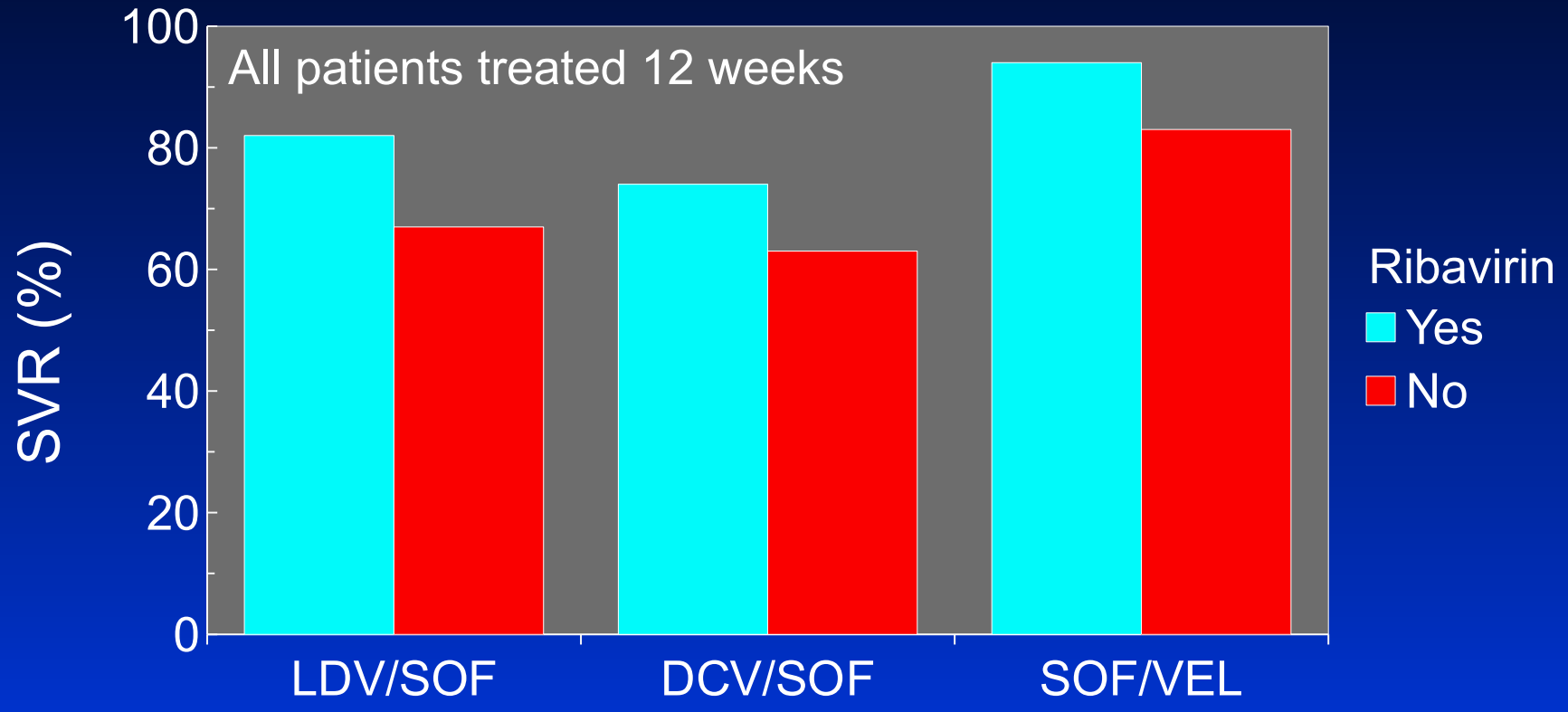
- Agents containing protease inhibitors cannot be used
  - Glecaprevir-piprentasvir
  - Sofosbuvir-velpatasvir-voxalaprevir
  - Elbasvir-grazoprevir
- Response rates lower than with no decompensation
- Using ribavirin increases SVR
- Complications of cirrhosis may interrupt treatment

HCV DECOMPENSATED CIRRHOSIS DURATION OF THERAPY



M Bourliere et al. Lancet Infect Dis. 2015;15:397-404.
MP Curry et al. N Engl J Med. 2015; 373:2618-2628.
M Charlton et al. Gastroenterol. 2015; 149:649-659.

HCV DECOMPENSATED CIRRHOSIS
ROLE OF RIBAVIRIN



CHILD CLASS: A-17%, B-73%, C-10% B: 100%

MCM Cheung et al. J Hepatol. 2016; 65:741-747.
MP Curry et al. N Engl J Med. 2015; 373:2618-2628.

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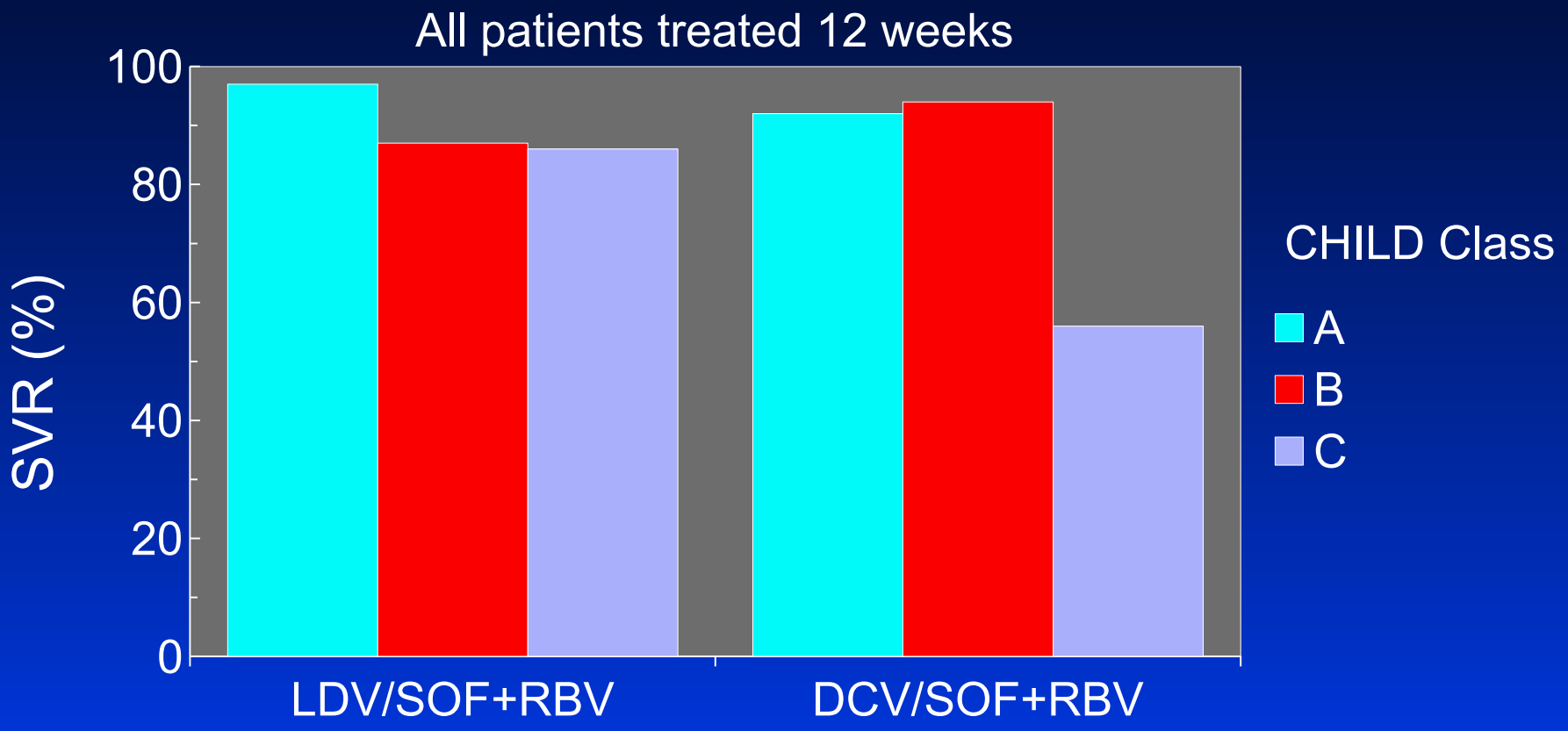
HCV DECOMPENSATED CIRRHOSIS DISEASE SEVERITY



N Afdhal et al. N Engl J Med. 2014; 370:1889-1898.
M Charlton et al. Gastroenterol. 2015; 149:649-659.
F Poordad et al. Hepatology. 2016; 63:1493-1505.

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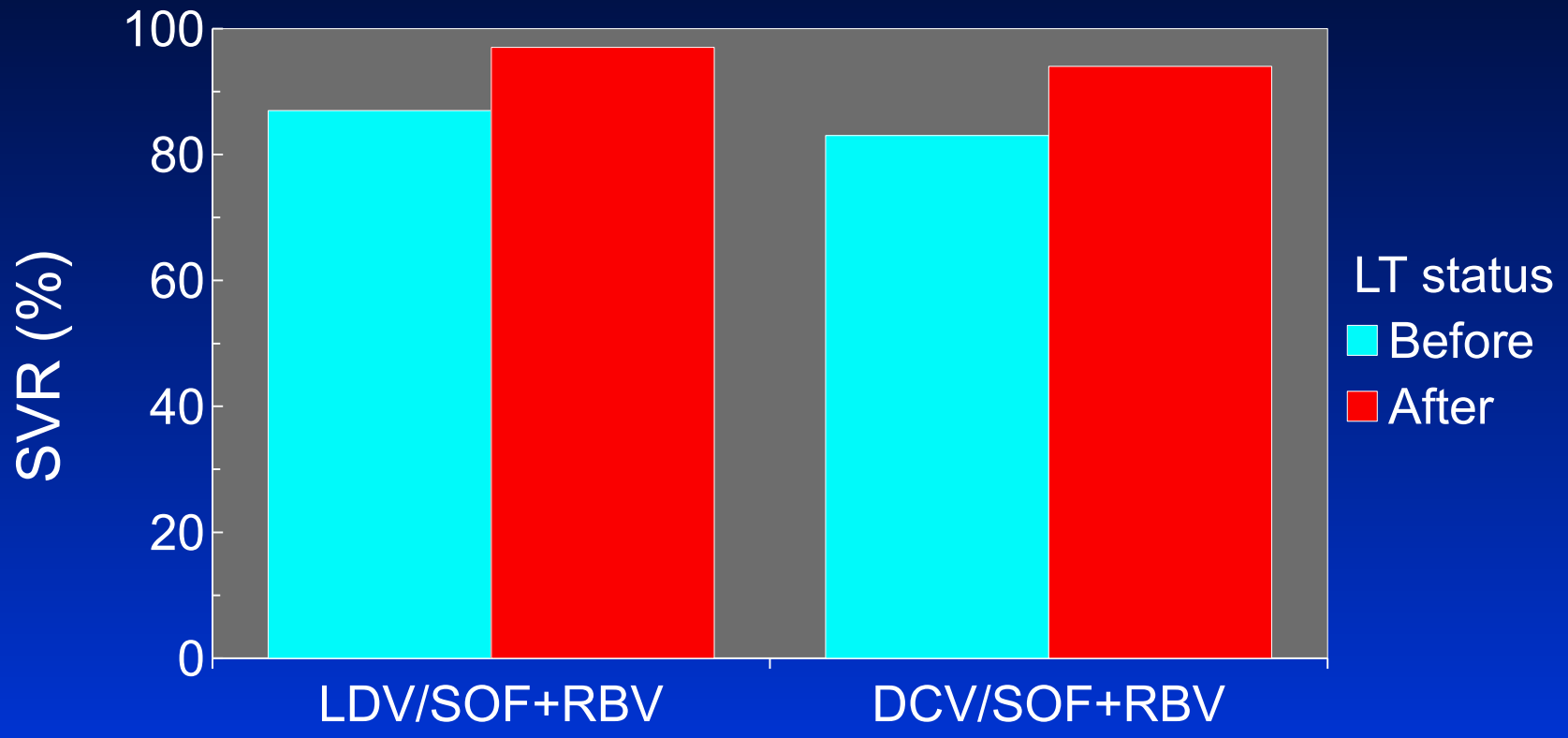
HCV DECOMPENSATED CIRRHOSIS LOWER SVR THAN AFTER LT



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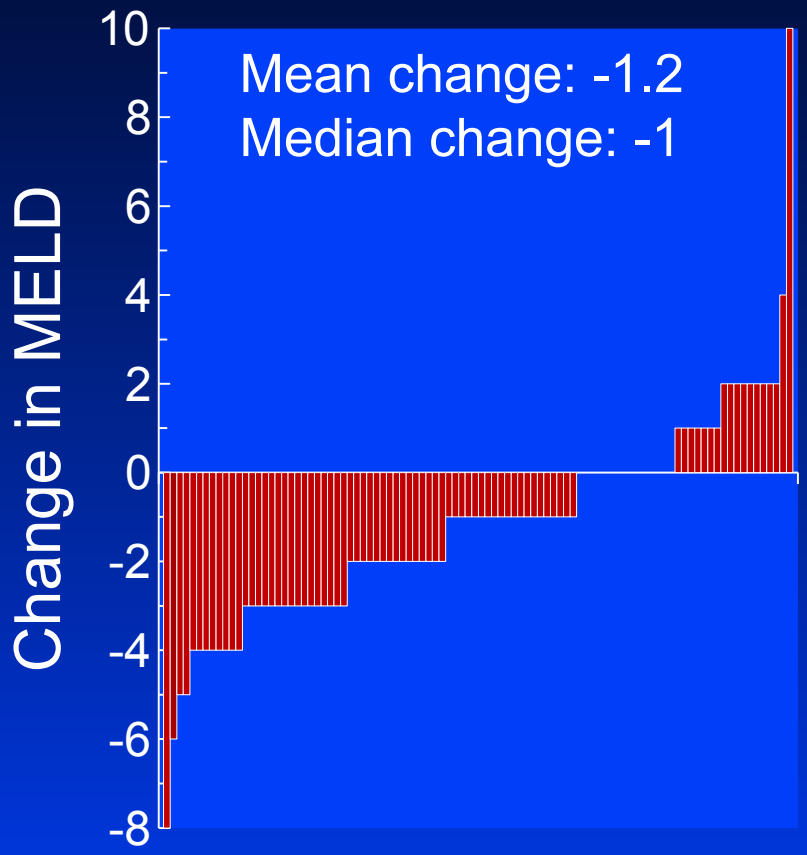
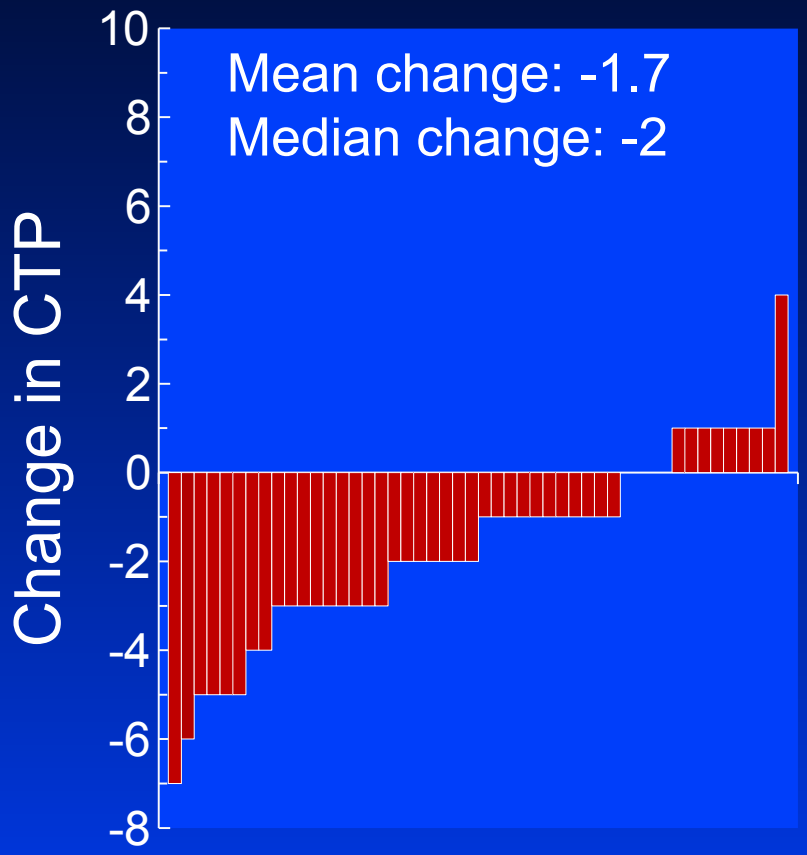
HCV DECOMPENSATED CIRRHOSIS
SVR IMPROVES LIVER FUNCTION





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Gastroenterol. 2015; 149:649-659.

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HCV DECOMPENSATED CIRRHOSIS DELISTING OF PATIENTS WITH SVR

MELD <16	MELD 16-20	MELD >20
25/51 = 49%	7/38 = 18%	2/13 = 15%
ΔMELD <2	ΔMELD <2	ΔMELD <2
9/33 = 27%	2/19 = 11%	0/8 = 0%
ΔMELD 2-4	ΔMELD 2-4	ΔMELD 2-4
12/14 = 86%	2/12 = 17%	0/1 = 0%
ΔMELD >4	ΔMELD >4	ΔMELD >4
4/4 = 100%	3/7 = 43%	2/4 = 50%

LS Belli et al
J Hepatol. 2016; 65:524-531.

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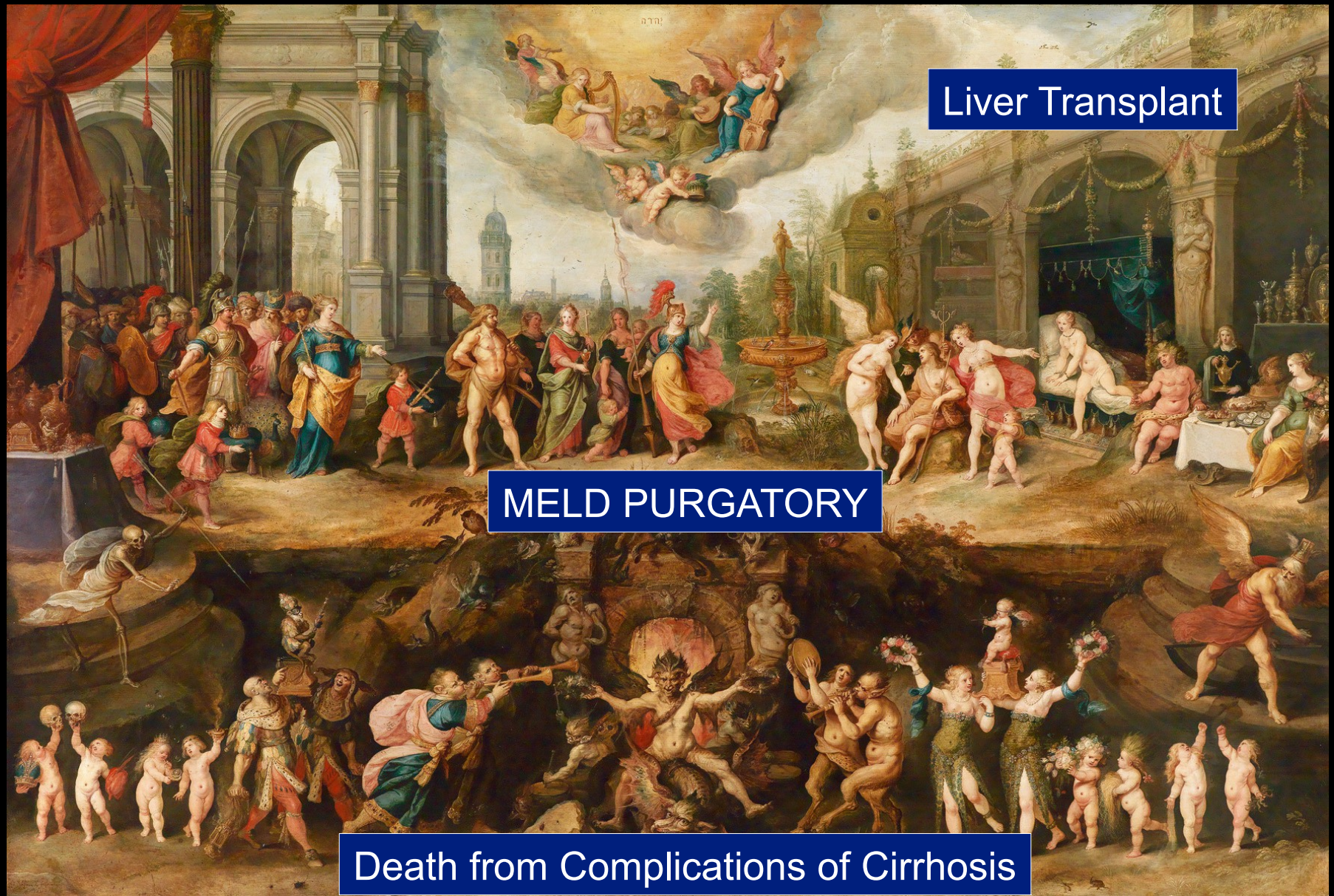
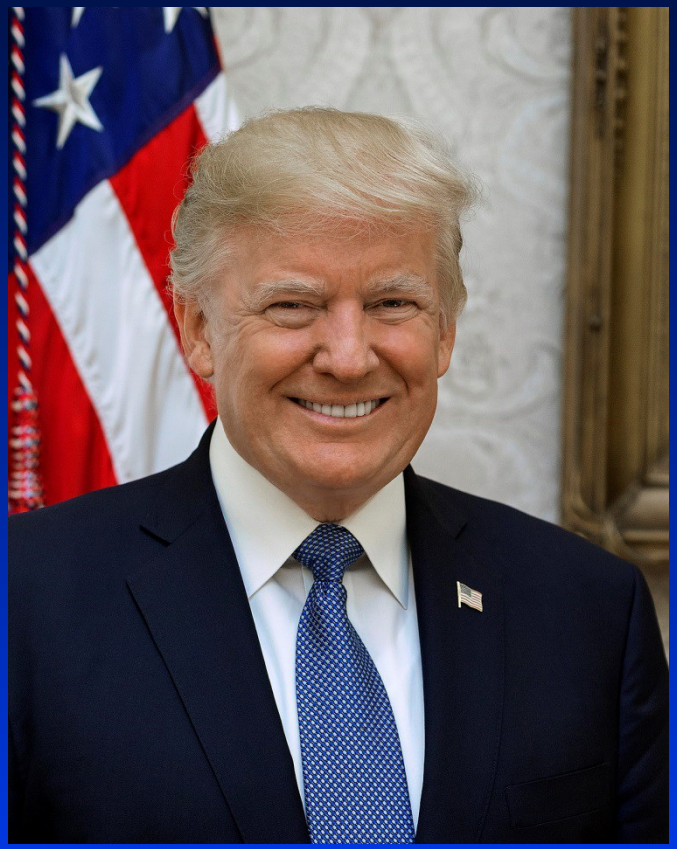
HCV DECOMPENSATED CIRRHOSIS OPTIONS

	Treat HCV	Liver Transplant
Pros	Cure HCV • Improve liver function • Reduce risk of HCC • Avoid transplantation	Eliminate cirrhosis Eliminate risk of HCC Higher HCV cure after LT
Cons	Lower cure rate Risk of HCC persists MELD purgatory • Cure SVR • Disease progression halted • MELD remains 16-20 • Cirrhosis symptoms persist	Prior to transplant: • Disease progression • Risk of decompensation • Risk of HCC • Risk of never getting a LT Post-LT: • Immune suppression • Other post-LT complications

FRANS FRANCKEN.
MAN CHOOSING BETWEEN VIRTUE AND VICE 1633.



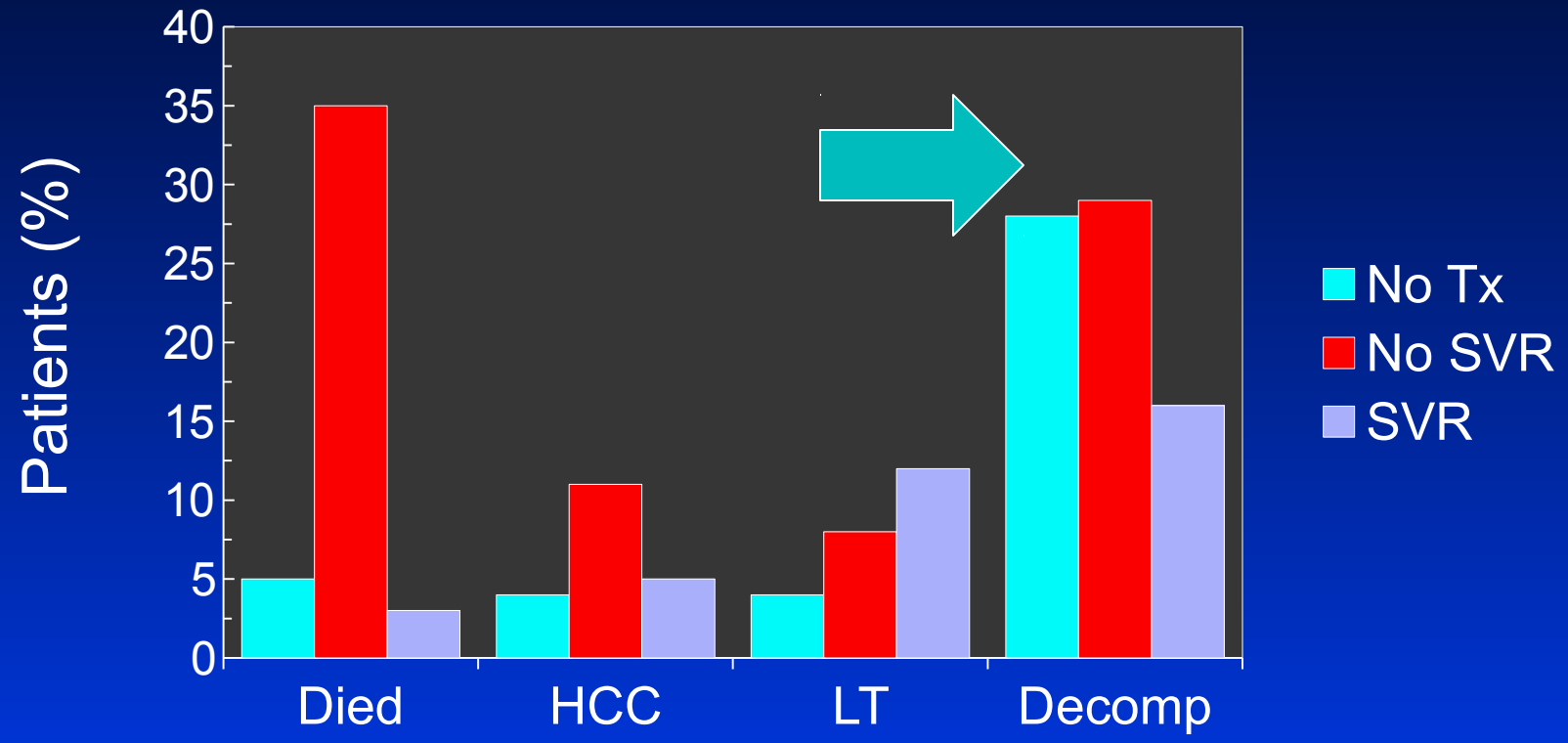
MELD PURGATORY
Modern Era Leader Dysfunction



HCV DECOMPENSATED CIRRHOSIS CASE

- Treated with Sofosbuvir-velpatasvir QD
  - Did not want to use RBV because HB 10 gm
  - Planned for 24 weeks of treatment
  - HCV RNA undetectable at week 4 and 12
  - Hospitalized with pneumonia, stage 4 HE at week 14
  - Physicians did not want to place NG tube because of previous variceal bleeding
  - Did not take DAA for 5 days
  - HCV RNA recurrence
  - Treatment stopped

HCV DECOMPENSATED CIRRHOSIS
FAILING DAA TREATMENT



MCM Cheung et al.
J Hepatol. 2016; 65:741-747.

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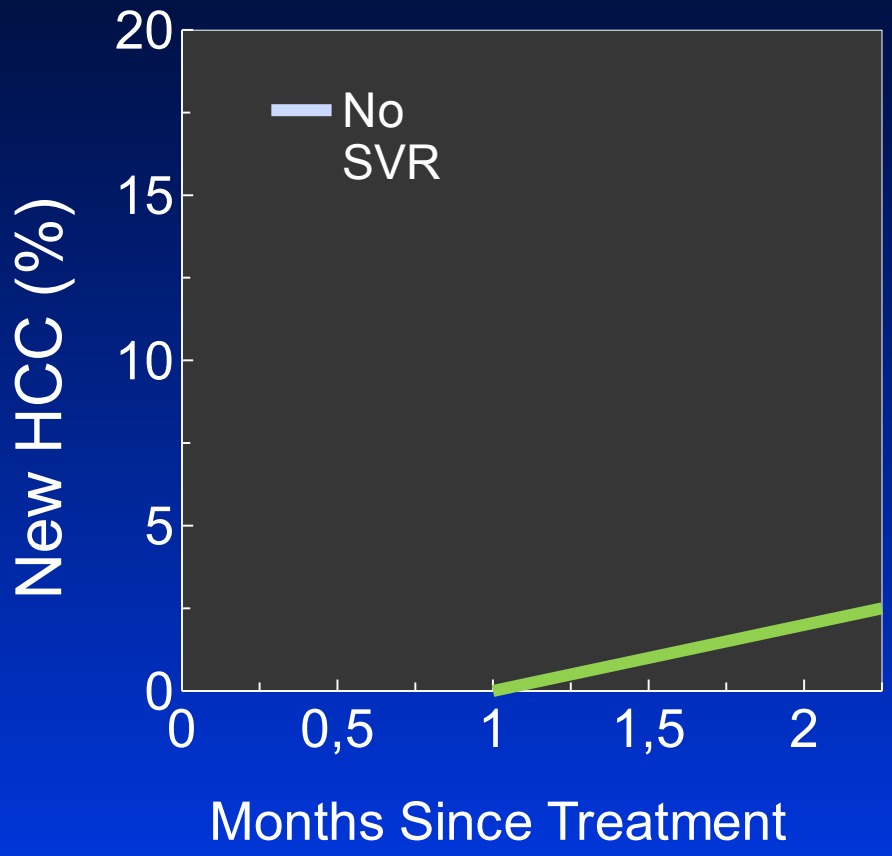
HCV DECOMPENSATED CIRRHOSIS CASE

- Evaluated and placed on LT waiting list with MELD 17
  - Agreed to accept an HCV positive donor
- Monitored every 3 months
  - Repeat EGD varices. Banding performed
  - Ultrasound to screen for HCC every 6 months
- 2017 (age 70 years)
  - 3 cm mass on routine ultrasound
  - AFP 121, L3 33%
  - Dynamic MRI 3.2 cm enhancing mass, with washout and delayed rim enhancement, right lobe, segment 6.

HCV DECOMPENSATED CIRRHOSIS
RISK OF NEW HCC AFTER DAA



	SVR	No SVR
N	4579	734
Decompensated	1942 26%	265 36%

Patients with more advanced cirrhosis have a lower SVR and a higher rate of developing HCC.
8% vs 4% per year

GN Iounnou et al
J Hepatol. 2018; 68:25-32.

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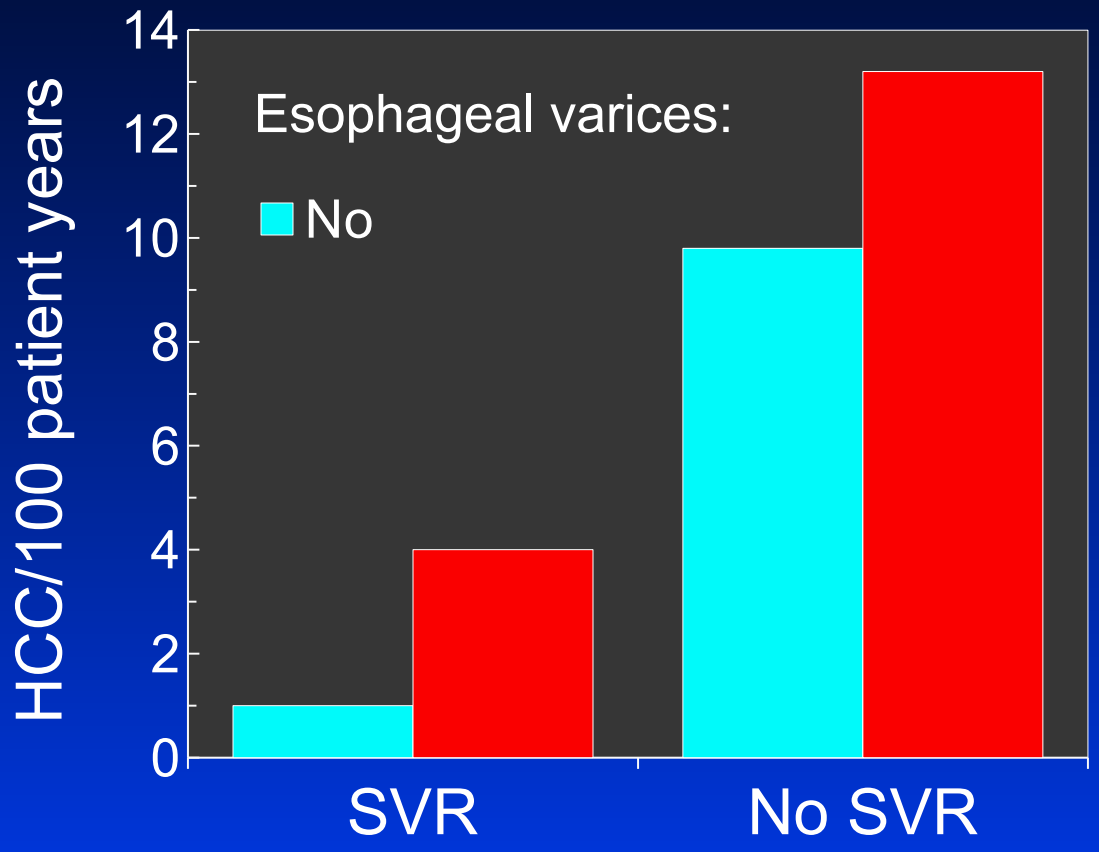
HCV DECOMPENSATED CIRRHOSIS
RISK OF NEW HCC AFTER DAA



- 1927 patients
- SVR in 95%
- 2 years monitoring
- 161 had prior HCC with HCC recurrence rate of 25%
- De Novo HCC developed in 2.8%
- Strongest predictors of HCC
  - No SVR
  - Esophageal varices

A Lleo et al.
EASL 2018; PS-154

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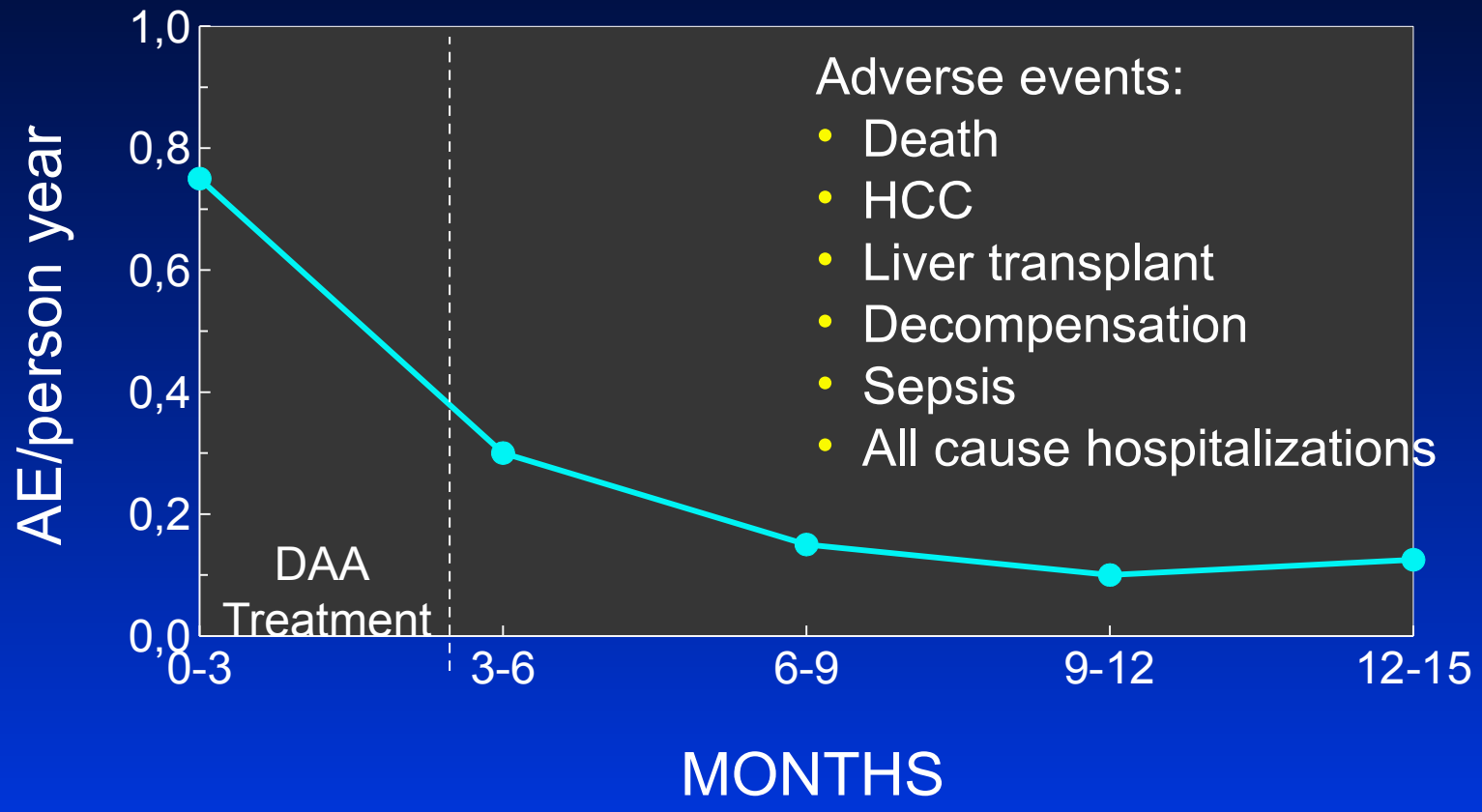
HCV DECOMPENSATED CIRRHOSIS CASE

- HCC treatment
  - TACE. 3 month MRI. Residual enhancement.
  - MWA. 3 month MRI. No enhancement. No new lesions.
- 2018 (age 71 years)
  - Mild muscle wasting
  - Step 2 diuretics, Lactulose and xifaxan
  - TBILI 3.3 mg/dl (56 umol/L), ALB 3.0 g/dl (30 gm/L)
  - NA 133, Scr 1.4 mg/dl (124 umol/L), NH3 55 umol/L
  - HB 12.0 g/dL (120 g/L), PLT 85,000, INR 1.5
  - MRI. No enhancing mass, patent PV, mild ascites
  - CTP 10, Child Class C, MELD 23

HCV DECOMPENSATED CIRRHOSIS CASE

- Treated with sofosbuvir-velpatasvir, ribavirin 600 mg QD for 12 weeks
- Achieved SVR
- 2019 (age 72 years)
  - No recurrence of HCC
  - Performance status improved
  - CTP 7, MELD 18
  - Removed for LT waiting list
  - Continues to be screened for HCC recurrence

HCV DECOMPENSATED CIRRHOSIS
ADVERSE EVENTS AFTER SVR



MCM Cheung et al.
J Hepatol. 2016; 65:741-747.

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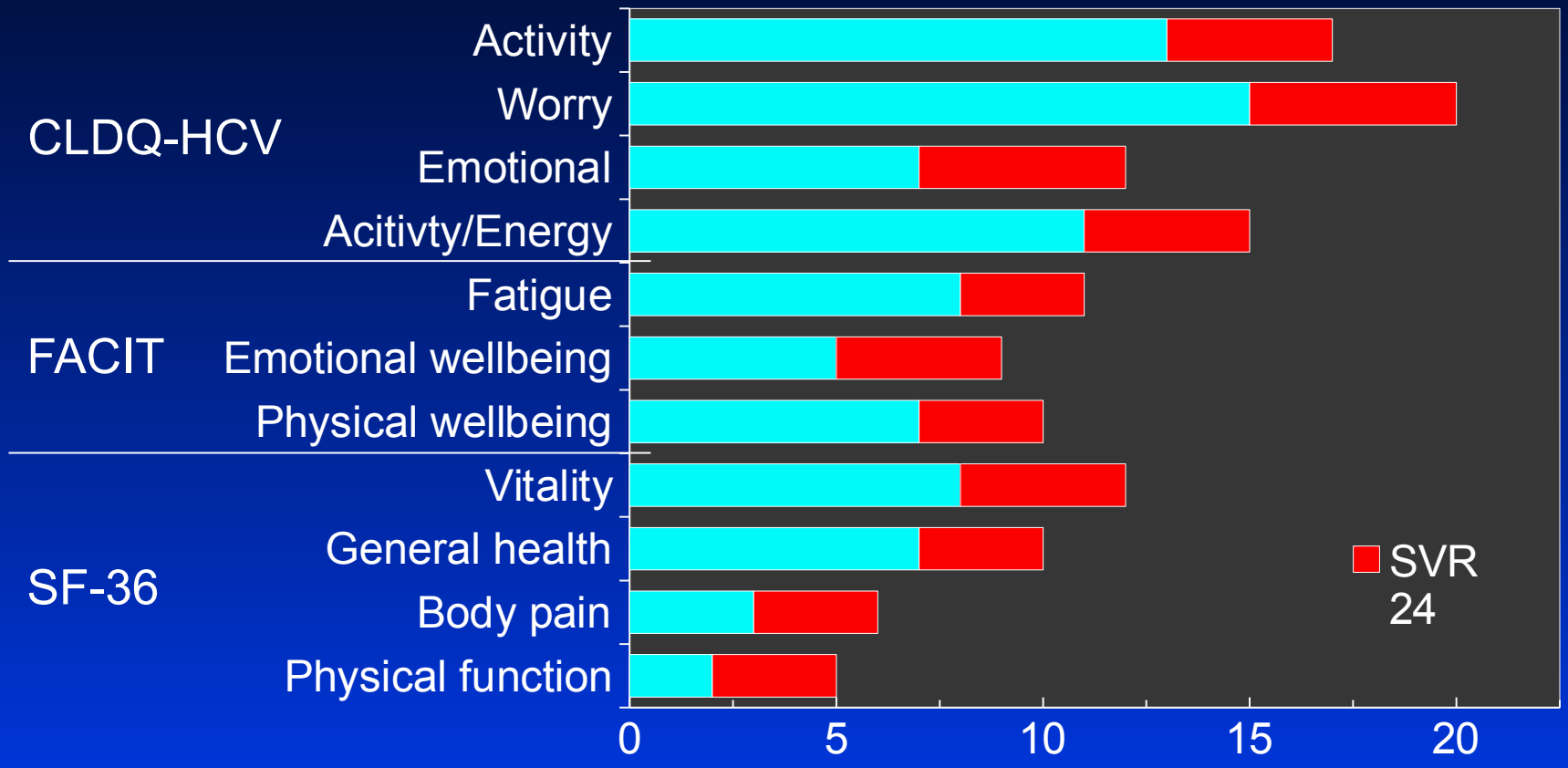
HCV DECOMPENSATED CIRRHOSIS
IMPROVEMENT IN PROs WITH SVR



ZM Younossi et al
Lancet 2016; 1:122-132.

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HCV DECEOMPENSATED CIRRHOSIS SUMMARY

Patients with HCV decompensated cirrhosis are the most difficult to manage
They are not hard to treat
They simply have too much baggage

Child Class B and C makes these patients slower
The SVR is about 10% lower
If hospitalized during treatment this may prevent closure
And the use of a PI is just not Kosher

HCV DECEOMPENSATED CIRRHOSIS SUMMARY

We thought we were rid of Ribavirin
But in decomp cirrhosis leaving it out is a sin
So we reluctantly retreat to a place we had been
To maximize SVR and achieve a big win

Treat or wait till OLT
Is the big question in decomp C
The risk is landing in place called MELD purgatory
Where HCV is cured but that's not the key
Because the patient feels bad and is in constant misery
Just hoping to develop a small HCC
So a liver transplant can set them free

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HCV DECEOMPENSATED CIRRHOSIS SUMMARY

But in patients who feel good and the MELD score is low
DAA treatment should be a go
Patients with SVR are happy…. Ho, Ho, Ho
The HCC risk declines and that makes us crow
And quality of life improves as measured by PRO

So managing HCV in decomp cirrhosis
Can lead you to develop neurosis
So step back and carefully consider the prognosis
Before you choose the option that's bogus