THE UNIVERSITY OF CHICAGO MEDICINE

# Controversies in Hepatitis C Management

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# Disclosures

**Gilead, AbbVie, Janssen, Merck, Novartis (grant support)**

# Can we eliminate HCV?

# Can we reduce and reverse end stage liver disease due to HCV?

# Everything You Need To Know

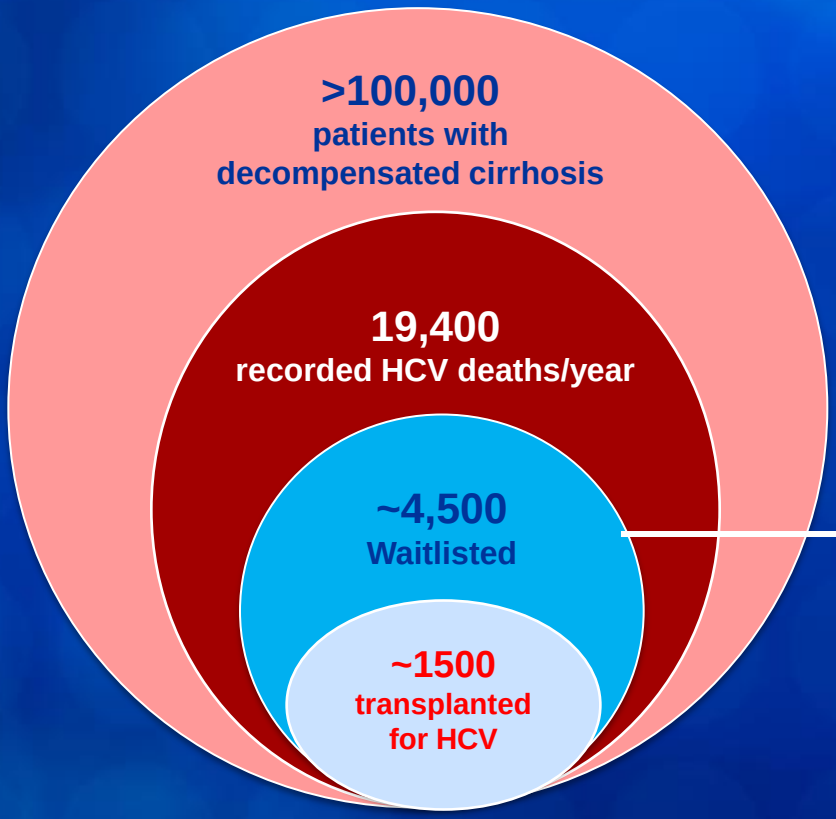


## www.hcvguidelines.org

# Areas of Controversy

- Who is too sick?
- Is there a benefit to treating patients with decompensated disease?

# Morbidity, Mortality And Transplantation Among HCV Infected Patients With Decompensated Cirrhosis In US




**1:5**
**Odds of dying or becoming too sick to transplant**

**1:3**
**Odds of being transplanted**

http://www.cdc.gov/hepatitis/Statistics/2013Surveillance/Table4.5.htm
http://onlinelibrary.wiley.com/doi/10.1111/ajt.13197/epdf
http://www.sciencedirect.com/science/article/pii/S001650850901885X#

# How can we eliminate HCV from the transplant environment?

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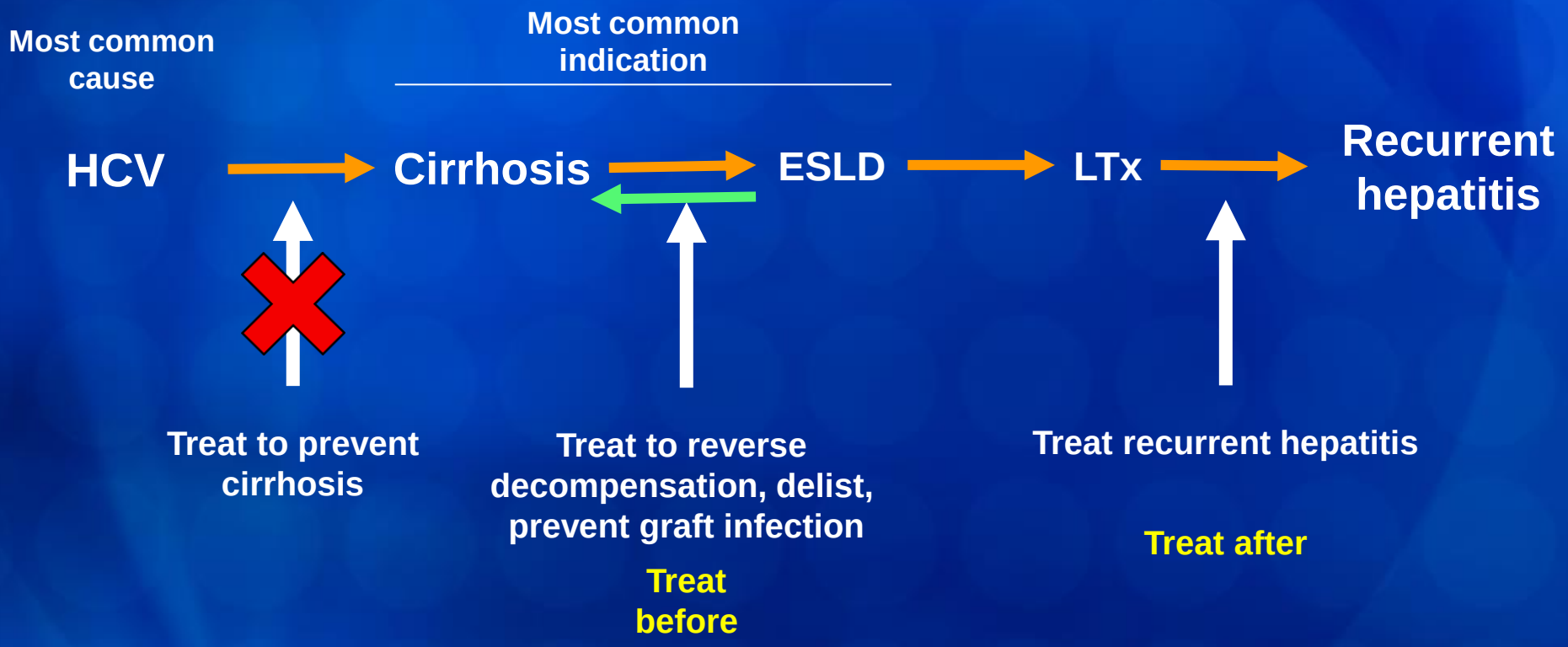
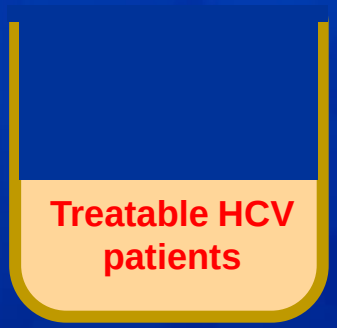


# DAAs have transformed management of HCV patients

**IFN-based therapy era**

**Patients ineligible for therapy**

- **Intolerant to IFN**
- **Intolerant to RBV**
- **Auto-immune hepatitis**
- **Severe heart disease**
- **Pregnant**
- **Mental health risk**
- **Severe hepatic dysfunction or decompensated cirrhosis**




**Chronic HCV-infected patients**

# We are now in the era where the majority of HCV-infected patients, including those with decompensated cirrhosis can be treated

2013 → 2017

## IFN-based therapy era

**Patients ineligible for therapy**

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- Mental health risk
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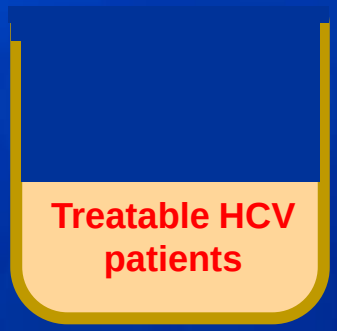



Chronic HCV-infected patients

## DAA therapy era

- Cirrhotic
- Co-morbidities
- Renal impairment
- Psychiatric
- Drug user
- Transplant
- Decompensated cirrhosis

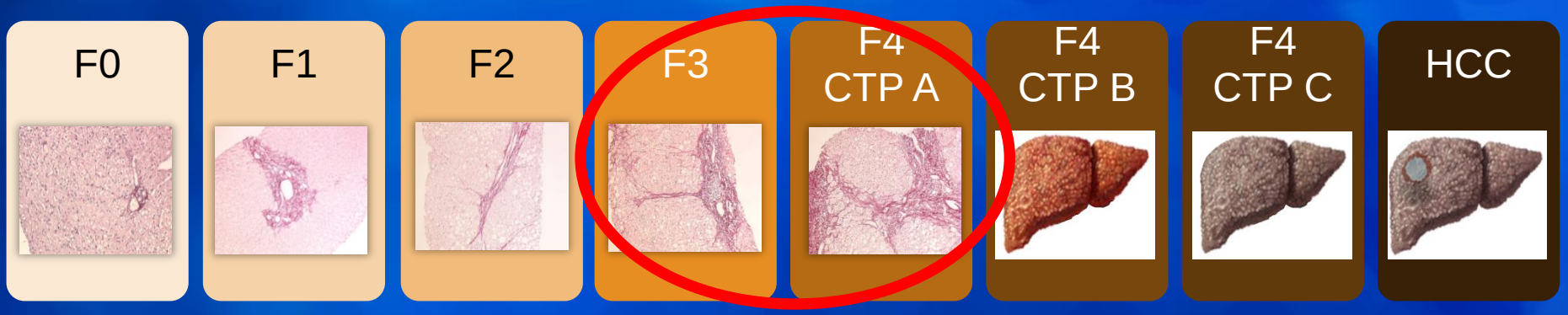
# Case

- 62 yr old man, white, Vietnam Vet
- HCV cirrhosis
- Mild ascites and encephalopathy
- MELD 25, albumin 2.8g/dl
- HCV relapse post IFN/RBV/TEL

# Case

- 62 yr old man, Vietnam Vet
- HCV cirrhosis
- Severe ascites and brittle HE
- MELD 32
- HCV relapse post IFN/RBV/TEL

# Improved efficacy and tolerability increases the populations we can treat

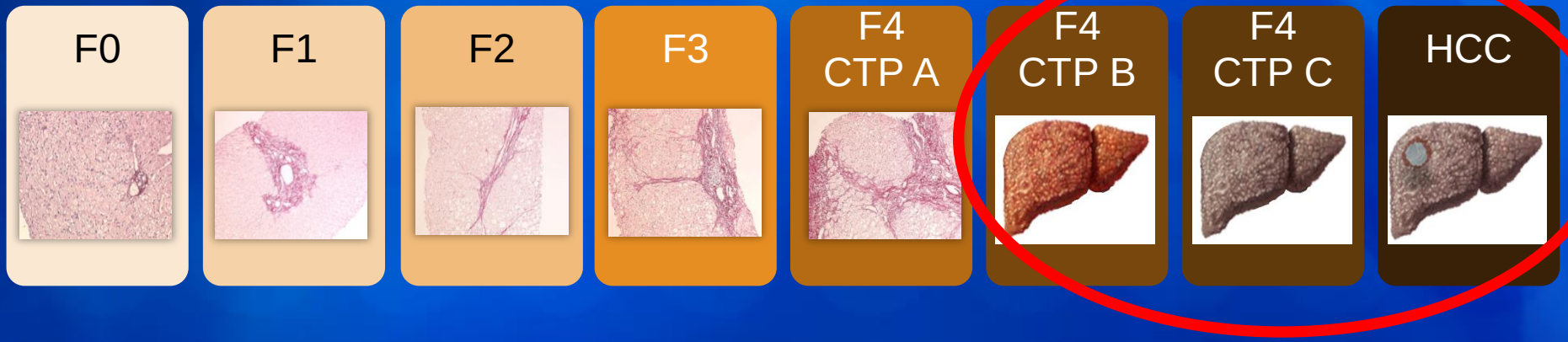



- **Previous therapy has been targeted to those at greatest need:**
  - **Advanced disease (F3/F4)**
  - **Severe extrahepatic manifestations/fatigue**

**Adapted from Asselah T, et al. J Hepatol 2014;61:193–5**

**CTP: Child–Turcotte–Pugh; F: fibrosis stage; GT: genotype; HCC: hepatocellular carcinoma**

# Improved efficacy and tolerability increases the populations we can treat




- Previous therapy has been targeted to those at greatest need:
  - Advanced disease (F3/F4)
  - Severe extrahepatic manifestations/fatigue
- New regimens are well tolerated in patients with advanced disease
  - Can they prevent death and need for liver transplant?

Adapted from Asselah T, et al. J Hepatol 2014;61:193–5

CTP: Child–Turcotte–Pugh; F: fibrosis stage; GT: genotype; HCC: hepatocellular carcinoma

# What drugs are safe?

| DAA Class | Name | $AUC_{24}$ (cf. healthy volunteers) | | |
|---|---|---|---|---|
| | | CTP A | CTP B | CTP C |
| NS3 PI | Simeprevir[2] | | 4X | 18X |
| | Paritaprevir[3] | 1.3 | 1.6 | 9.2 |
| | Grazoprevir[4] | 1.2 | 5.0 | 19.8 |
| NS5AI | Daclatasvir[5] | – | 0.98 | 0.95 |
| | Ledipasvir[6] | – | 1.0 | 1.1 |
| | Ombitasvir[3] | 0.9 | 0.7 | 0.5 |
| | Elbasvir[7] | 0.8 | 0.9 | NA |
| | velpatasvir | – | 1.0 | 1.1 |
| Non-NUC NS5B | Dasabuvir[3] | 1.2 | 0.8 | 4.2 |
| NUC NS5B I | Sofosbuvir[1] | – | 1.2 | 1.1 |


[1]Lawtitz E, et al. EASL 2012
[2]Ouwerkerk-Mahadevan S, et al. 8th Int Workshop Clinical Pharm Hep Therapy, 2013
[3]Khatri A, et al. AASLD 2012; [4]Yeh W, et al. EASL 2014
[5]Bifano M, et al. AASLD 2011; [6]German P, et al. AASLD 2013
[7] Marshall W, et al. 15th Int Workshop Clinical Pharm Hep Therapy, 2014

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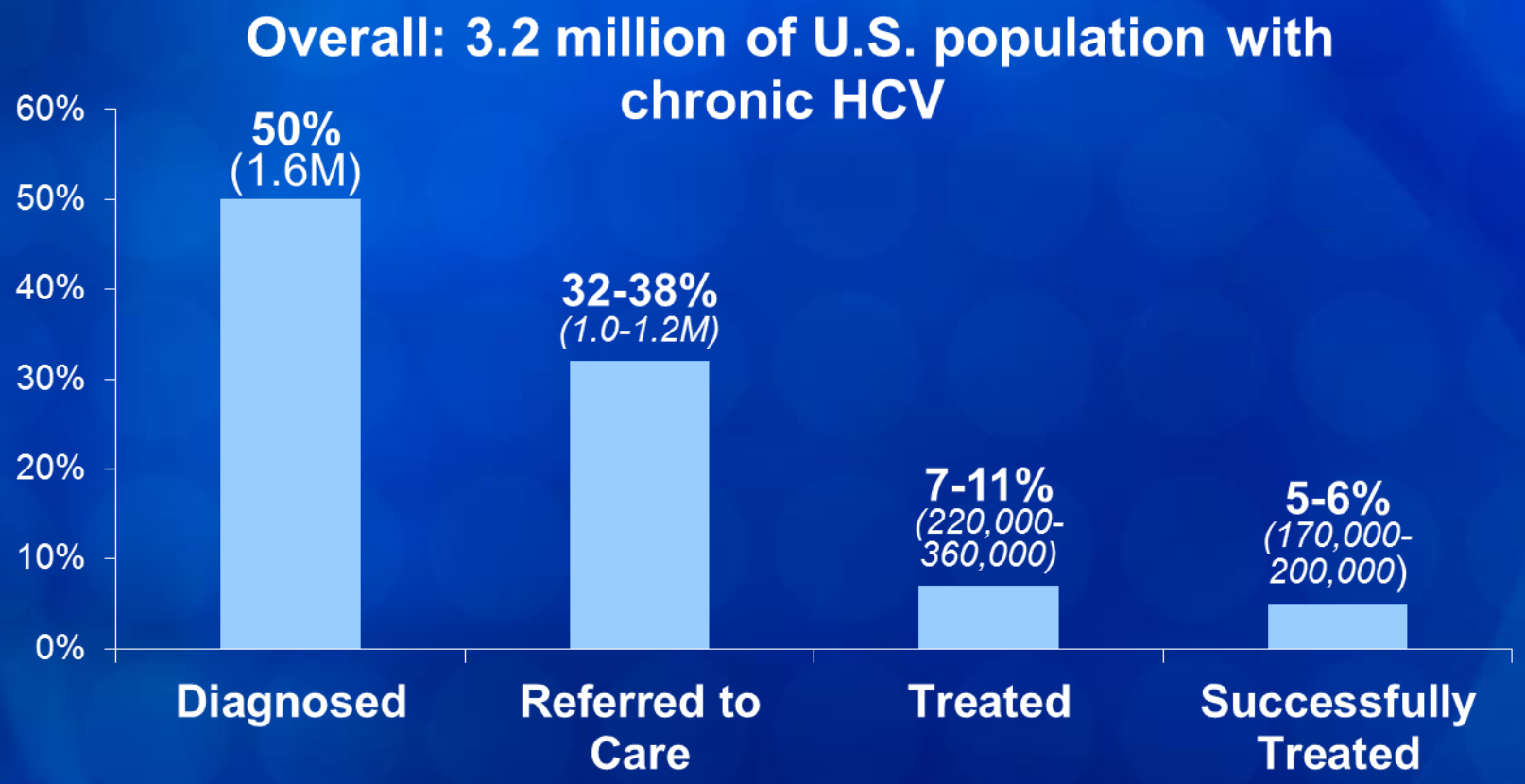
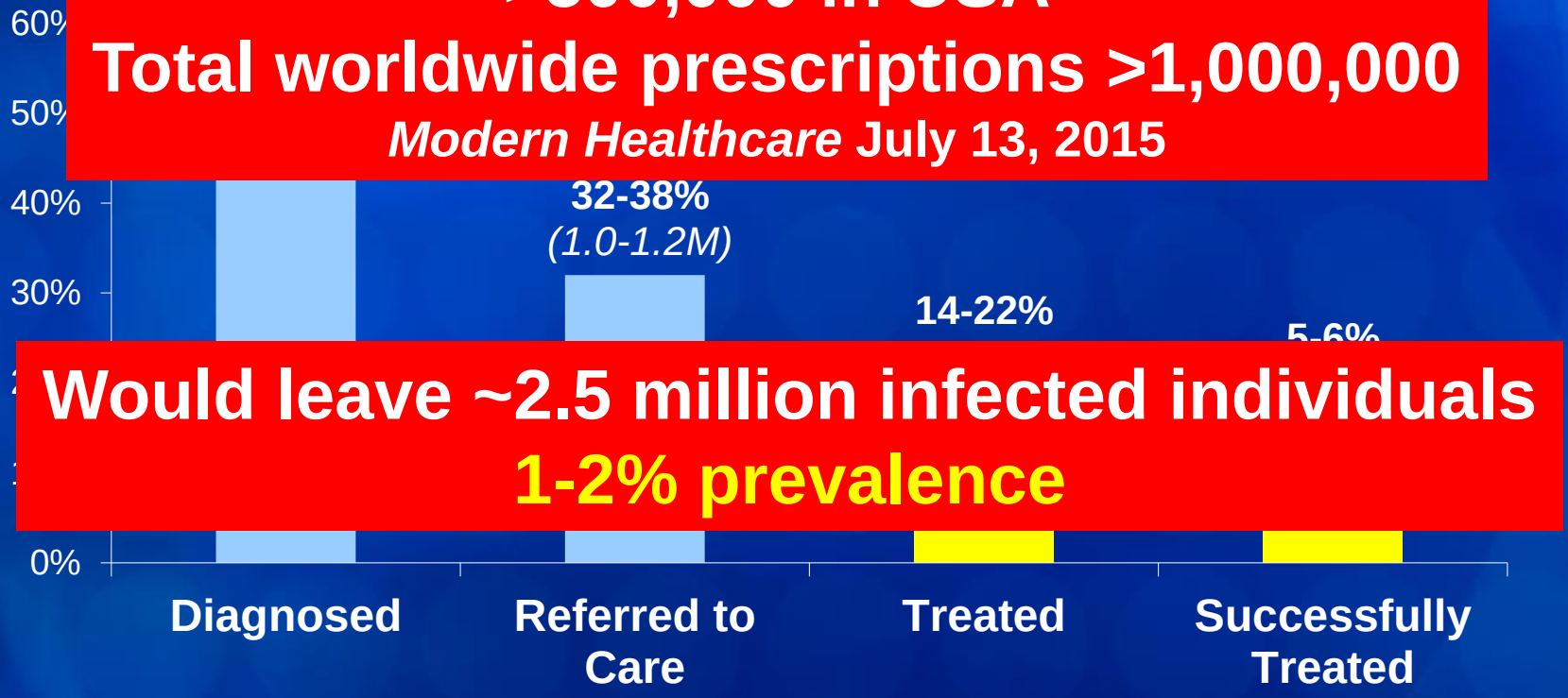
# Impact of Direct Acting Antivirals on Frequency of Treatment Utilization




Holmberg SD et al. *New Engl J Med*. 2013;368:1859-1861.

# Impact of Direct Acting Antivirals on Frequency of Treatment Utilization

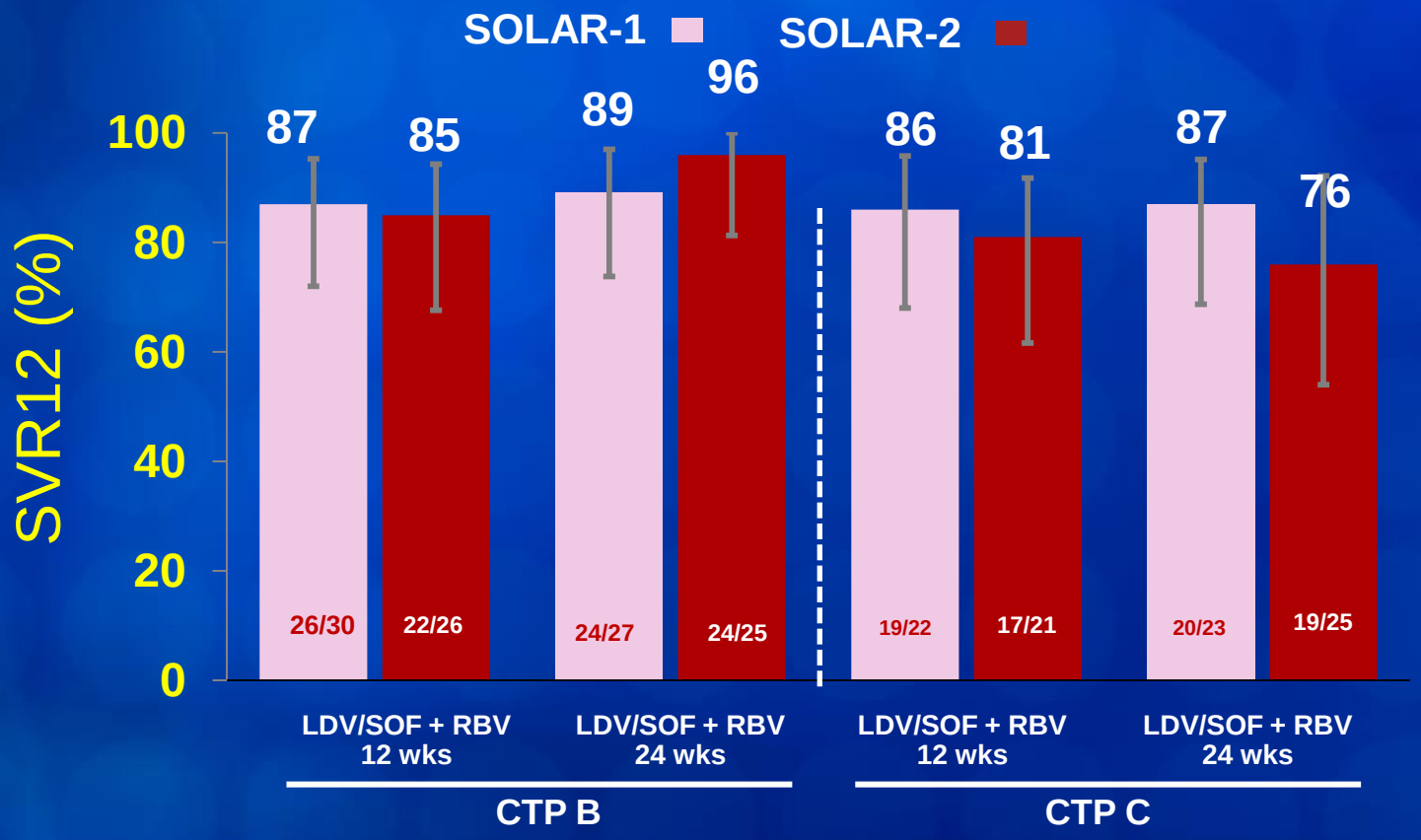
**Number of DAA prescriptions:**
**>500,000 in USA**
**Total worldwide prescriptions >1,000,000**
***Modern Healthcare* July 13, 2015**




**Would leave ~2.5 million infected individuals**
**1-2% prevalence**

Holmberg SD et al. *New Engl J Med*. 2013;368:1859-1861.

# SOLAR-1/2: Overall Efficacy Pre-LTx in GT 1 and GT 4




**Comparable efficacy between SOLAR-1 and SOLAR-2 studies**

Charlton M, et al. Gastroenterology 2015;149:649–59;
Manns M, et al. Lancet Infect Dis 2016;16:685–97

Error bars represent 90% confidence intervals

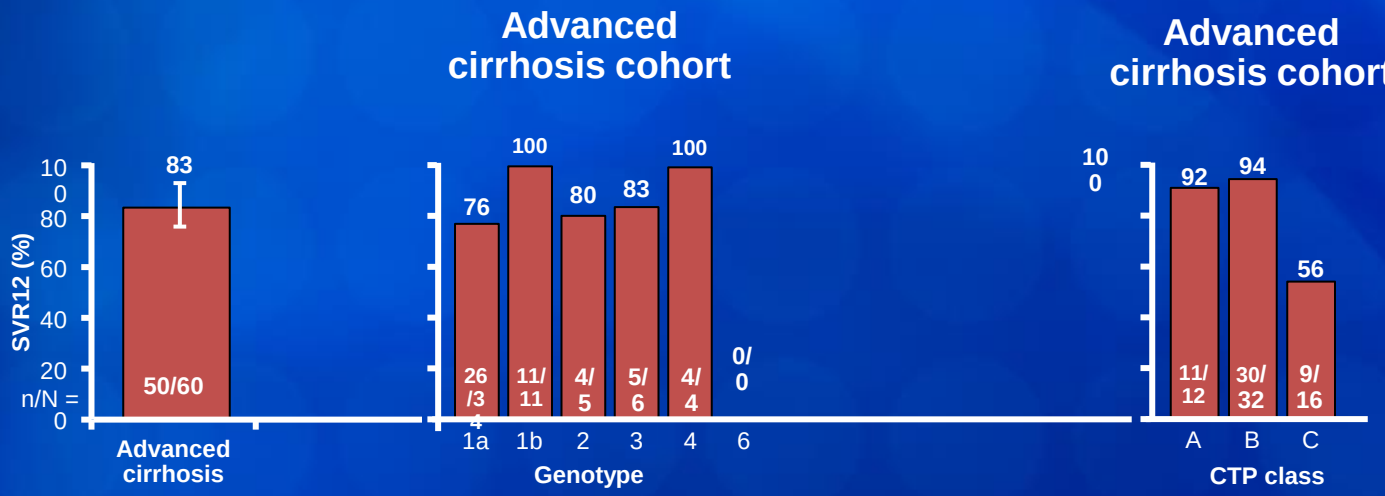
# SOLAR-1/2: Overall pre-LTx Safety Summary

| | Pre-Transplant |
|---|---|
| **Patients, n (%)** | **CTP B + C (n=215)** |
| Any AE | 208 (97) |
| Grade 3–4 AE | 51 (24) |
| Serious AE | 61 (28) |
| Serious treatment-related AE | 5 (2) |
| AE leading to D/C of LDV/SOF | 9 (4) |
| Death | 10 (5) |
| Rejection episode | 0 |
| Graft loss | 1 |
| Liver transplantation | 11 |

- **Treatment-related SAEs were mostly related to RBV treatment**
- **Deaths and AEs that led to D/C of LDV/SOF were not attributed to study treatment**

**Samuel D, et al. EASL 2015, P0774**

# ALLY-1: SOF + DCV in advanced cirrhosis




- In subgroup analysis of patients in the advanced cirrhosis group, those who were CTP class C (n = 16) or had albumin < 2.8 g/dL (n = 18) had SVR12 rates of 56%
- 10/10 patients who relapsed in the advanced cirrhosis group had NS5A RASs at virological failure; 4 of 10 patients had NS5A RASs at baseline

RAS: resistance-associated substitution

Poordad F, et al. Hepatology 2016;63:1493−1505

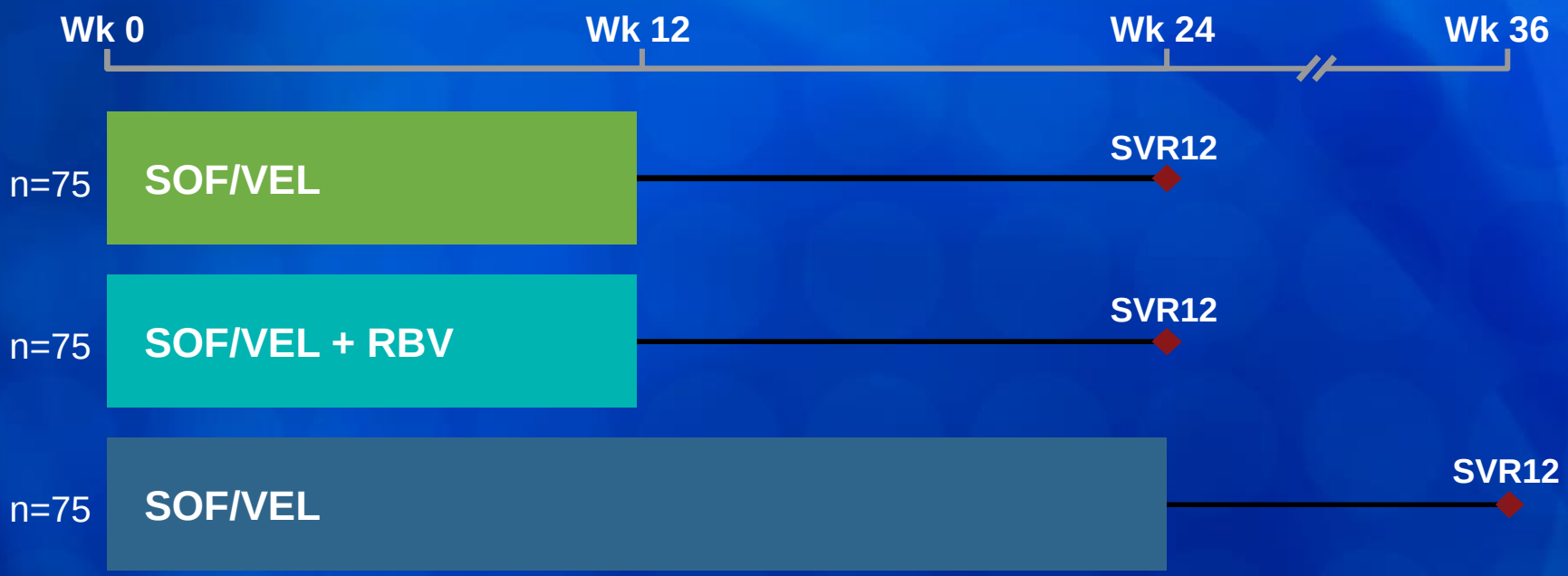
# Sofosbuvir/Velpatasvir Fixed-Dose Combination for the Treatment of HCV in Patients With Decompensated Liver Disease: the Phase 3 ASTRAL-4 Study

M.P. Curry,[1] J.G. O'Leary,[2] N.H. Bzowej,[3] A.J. Muir,[4] K.M. Korenblat,[5] J.M. Fenkel,[6] K.R. Reddy,[7] E. Lawitz,[8] T.D. Schiano,[9] L.W. Teperman,[10] R.J. Fontana,[11] E.R. Schiff,[12] M.W. Fried,[13] B. Doehle,[14] D. An,[14] J. McNally,[14] A. Osinusi,[14] M. Natha,[14] D.M. Brainard,[14] J.G. McHutchison,[14] R.S. Brown,[15] M.R. Charlton[16]

[1]Intermountain Medical Center, Murray, UT; [2]Baylor Research Institute, Dallas, TX; [3]Ochsner Medical Center, New Orleans, LA; [4]Duke University, Durham, NC; [5]Washington University School of Medicine in Saint Louis, MO; [6]Thomas Jefferson University, Philadelphia, PA; [7]University of Pennsylvania School of Medicine, Philadelphia, PA; [8]Texas Liver Institute, San Antonio, TX; [9]Mount Sinai Hospital, New York, NY; [10]NYU School of Medicine, New York, NY; [11]University of Michigan, Ann Arbor, MI; [12]University of Miami, Coral Gables, FL; [13]University of North Carolina at Chapel Hill School of Medicine; [14]Gilead Sciences, Inc., Foster City, CA; [15]Columbia University Medical Center, New York-Presbyterian, New York, NY; [16]Beth Israel Deaconess Medical Center, Boston, MA

*N Engl J Med.* 2015 2015; 373:2618-2628

# Study Design




SVR12, sustained virologic response 12 weeks after treatment end.

- Open-label, randomized (1:1:1) US study (NCT02201901)
- HCV GT 1–6 treatment-naïve or -experienced patients with Child-Pugh-Turcotte (CPT) B cirrhosis
- Key eligibility criteria: creatinine clearance ($CL_{cr}$) >50 mL/min, platelets >30,000/$mm^3$; no hepatocellular carcinoma or liver transplant

# ASTRAL-4: Baseline Liver Disease Characteristics

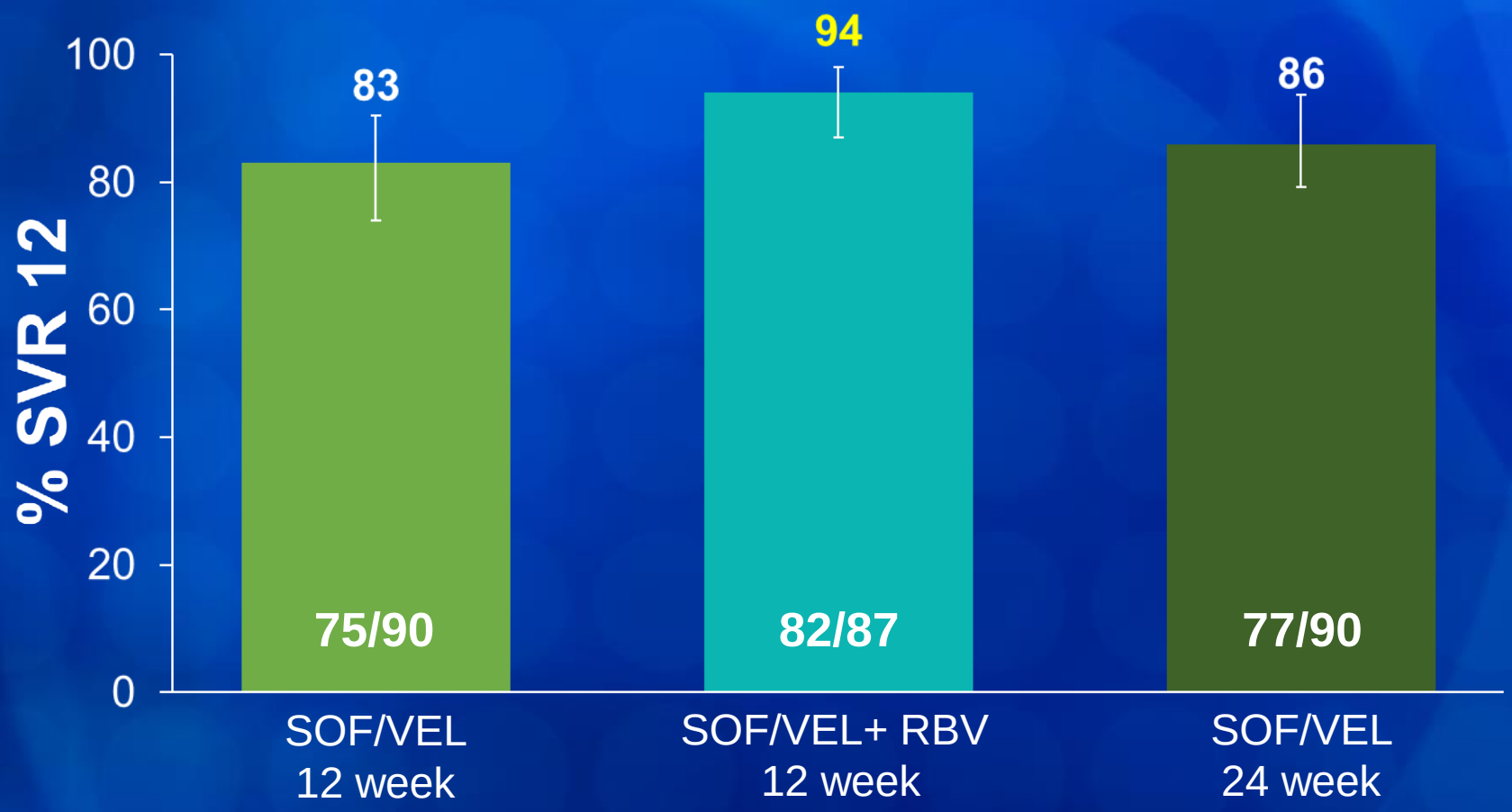

| Patients | SOF/VEL 12 wk n=90 | SOF/VEL+RBV 12 wk n=87 | SOF/VEL 24 wk n=90 |
|---|---|---|---|
| Ascites, n (%) | 74 (82) | 65 (75) | 75 (83) |
| Encephalopathy, n (%) | 52 (58) | 54 (62) | 59 (66) |
| Median total bilirubin, mg/dL (range) | 1.3 (0.3–4.5) | 1.5 (0.3–4.3) | 1.6 (0.3–9.3) |
| Median albumin, g/dL (range) | 3.2 ( 2.2–4.2) | 3.1 (2.1–4.4) | 3.1 (2.3–4.3) |
| Median INR (range) | 1.2 (0.9–1.7) | 1.2 (0.9–1.8) | 1.2 (0.9–1.6) |

**INR, international normalized ratio.**

*N Engl J Med* 2015; 373:2618-2628

# Overall SVR12

The NEW ENGLAND JOURNAL of MEDICINE




**P-value < 0.001 for comparison of SVR12 rate to 1% for each treatment group**
**Error bars represent 95% confidence intervals.**

*N Engl J Med* 2015; 373:2618-2628

# SVR12 in GT 3 Patients

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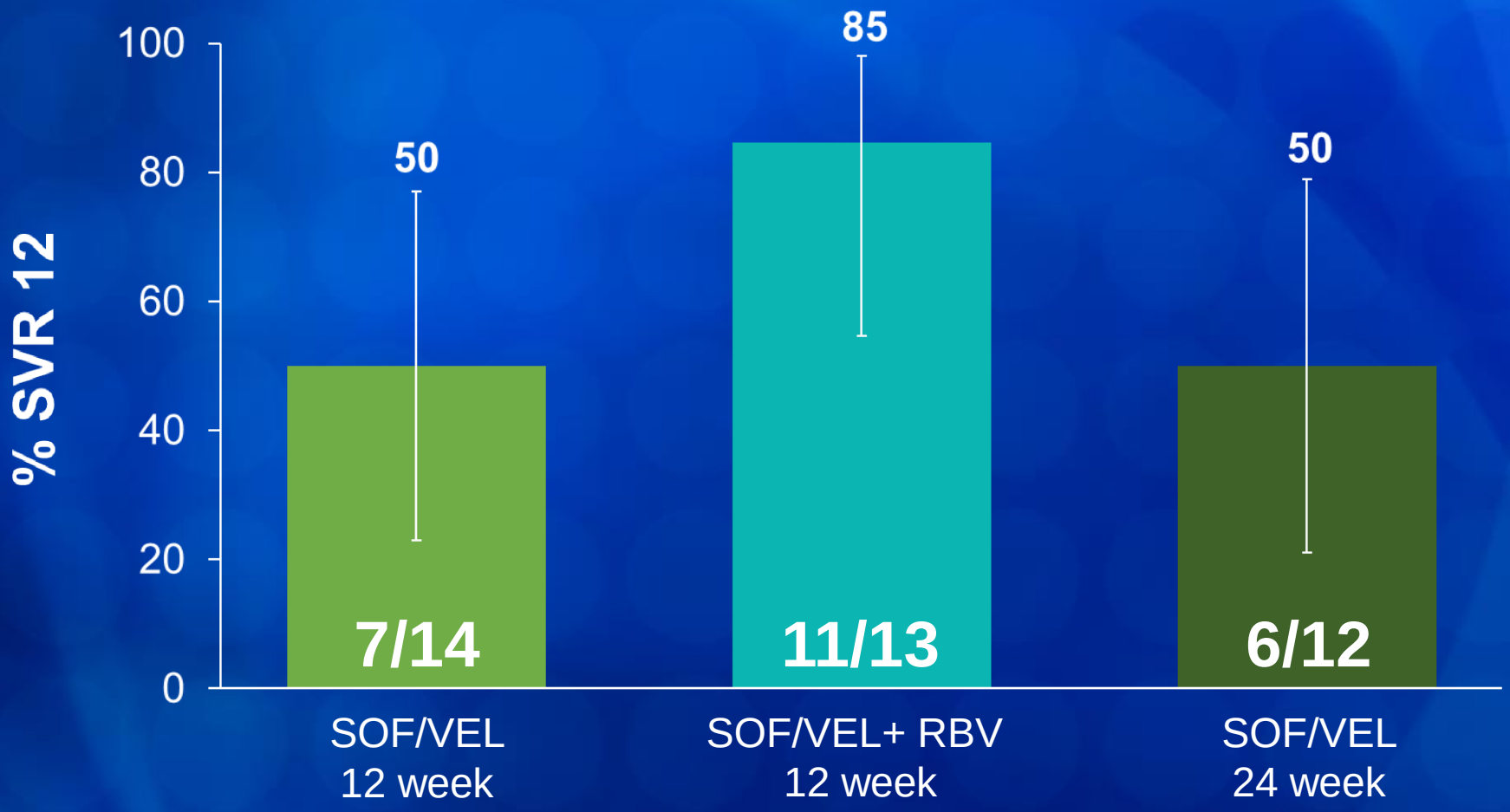
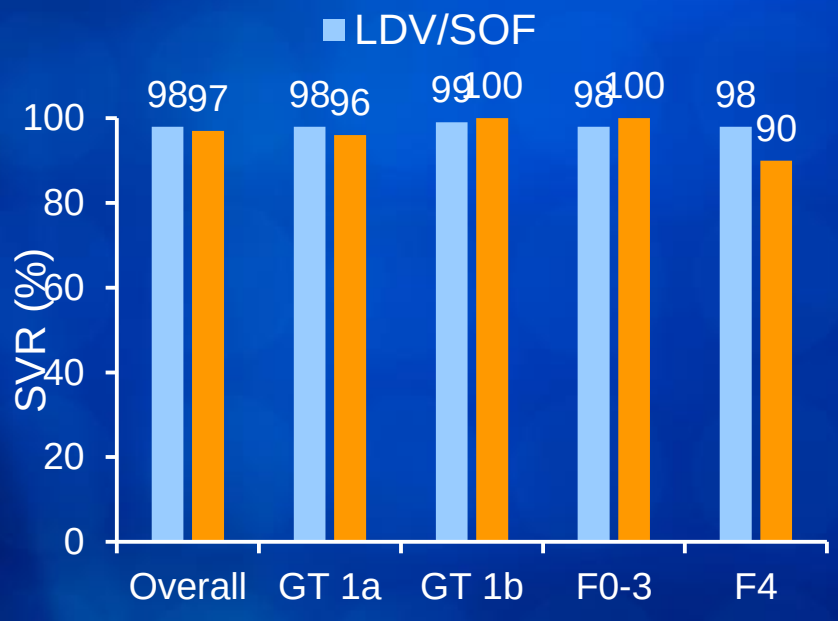



Error bars represent 95% confidence intervals.

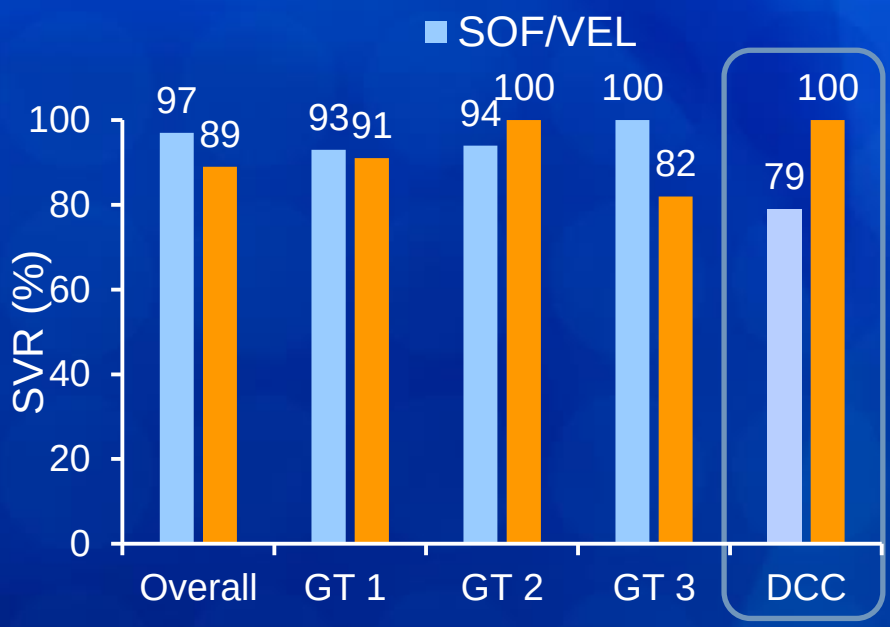
*N Engl J Med* 2015; 373:2618-2628

# Efficacy of SOF-based therapy in the real world: an update from ILC 2017

**Real world experience with 12-week regimens from the TRIO network[1]**




**Real world experience from the TARGET network[2]**



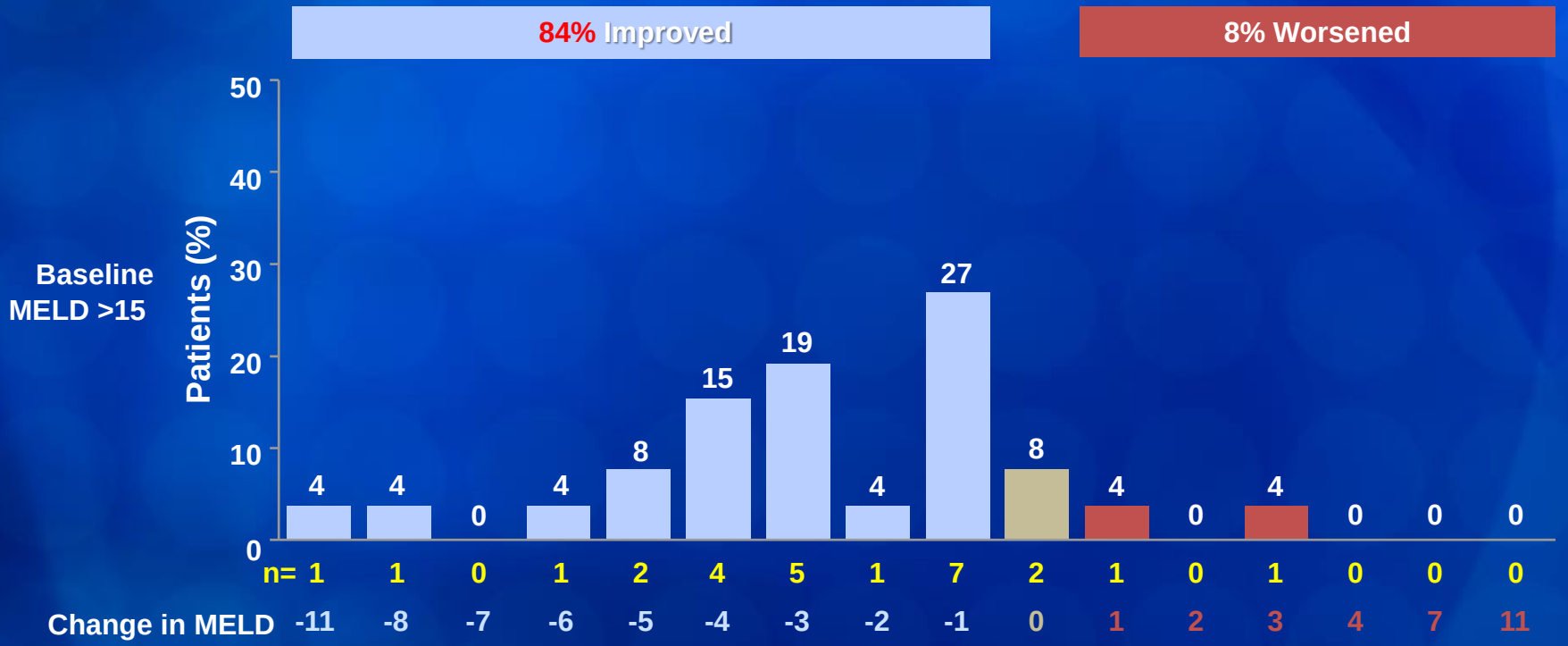

**The safety profile of SOF/VEL ± RBV in real world studies was similar to that in clinical trials[2]**


1.Tsai N et al. ILC 2017 SAT #244
2.Khalili M, et al. ILC 2015 SAT #222

# Do patients with decompensated liver disease get better with treatment?

# MELD Change: Baseline to Follow-up Week 12 Patients With SVR12

The NEW ENGLAND JOURNAL of MEDICINE



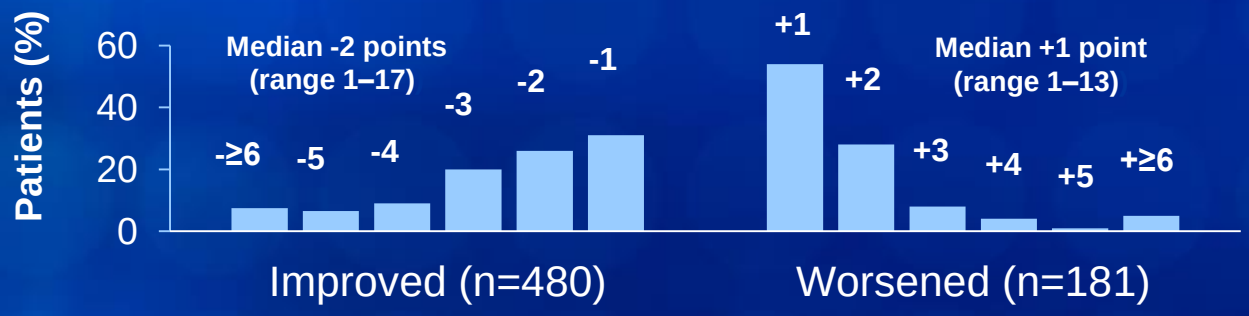

No follow-up Week 12 assessment for 5 patients.

*N Engl J Med* 2015; 373:2618-2628

# DAAs before LTx: treat to improve liver function

**Changes in MELD scores following DAA treatment in patients with decompensated cirrhosis**

| Regimen | n* | SVR | Improved | Unchanged | Worsened |
|---|---|---|---|---|---|
| LDV/SOF + RBV | 94 | 87% | 63 (67%) | 15 (16%) | 16 (17%) |
| LDV/SOF + RBV | 136 | 83% | 96 (71%) | 18 (13%) | 22 (16%) |
| SOF + DCV + RBV | 56 | 83% | 25 (45%) | 12 (21%) | 19 (34%) |
| SOF + NS5A ± RBV | 220 | 75% | 134 (61%) | 33 (15%) | 53 (24%) |
| GRZ/EBV | NOT RECOMMENDED | | | | |
| SOF/VEL ± RBV | 250 | 88% | 136 (54%) | 52 (21%) | 62 (25%) |
| SOF + DCV + SMV | NOT RECOMMENDED | | | | |
| Total | 801 | 83.5%† | **480 (60%)** | **140 (17%)** | **181 (23%)** |

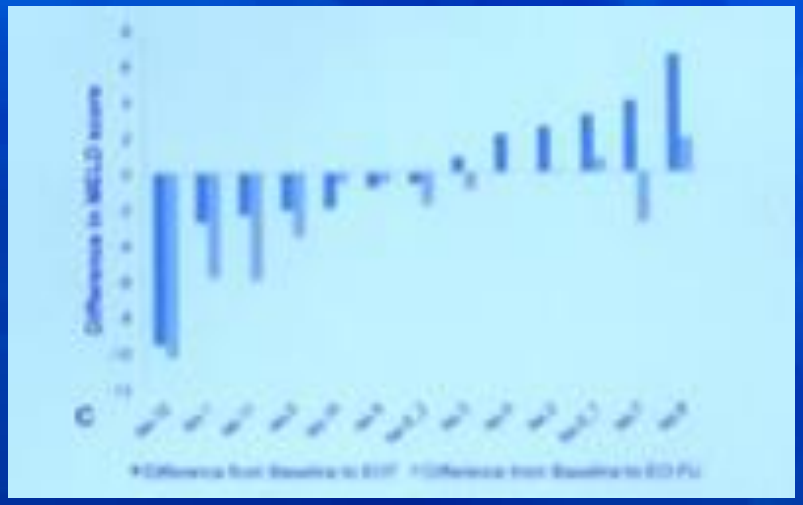


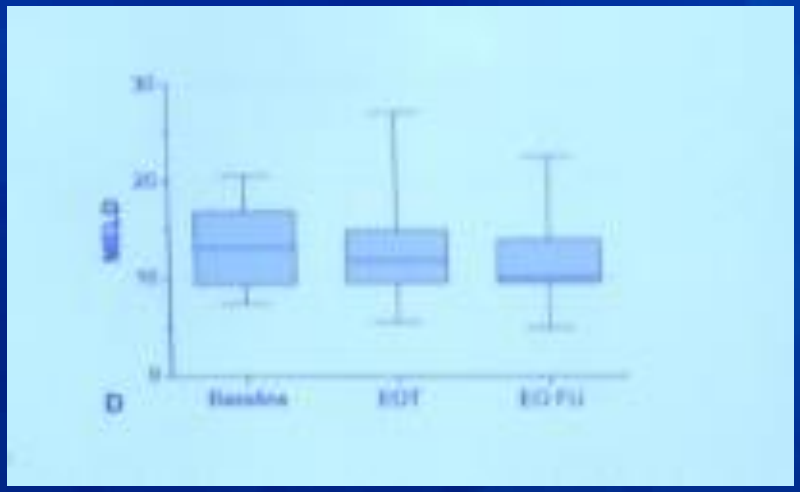

Bunchorntavakul C et al. J Viral Hepat 2016;23:408-4189

*Estimated number of patients with decompensated cirrhosis who were treated and had available MELD scores at post-treatment Weeks 4–12; †Average SVR rate (weighted by number of patients of each study).
EBV: elbasvir; GRZ: grazoprevir; SMV: simeprevir

# Real world experience of DAAs in HIV-HCV Co-infected patients on the transplant list

- HIV/HCV co-infected patients (n=12) received DAAs on waiting list [1]
  - 50% CTP A; 50% (CTP B or CTP C)
  - Median MELD: 12
  - IFN-experienced (n=8)
- Treatment regimens
  - SOF + DCV, 12/24 weeks (n=6)
  - LDV/SOF + RBV, 12/24 weeks (n=2)
  - SOF + RBV, 24/27 weeks (n=2)
  - OMV/PTV/RTV + DSV, 24 weeks (n=1)
- 92% SVR; 1 patient LTx

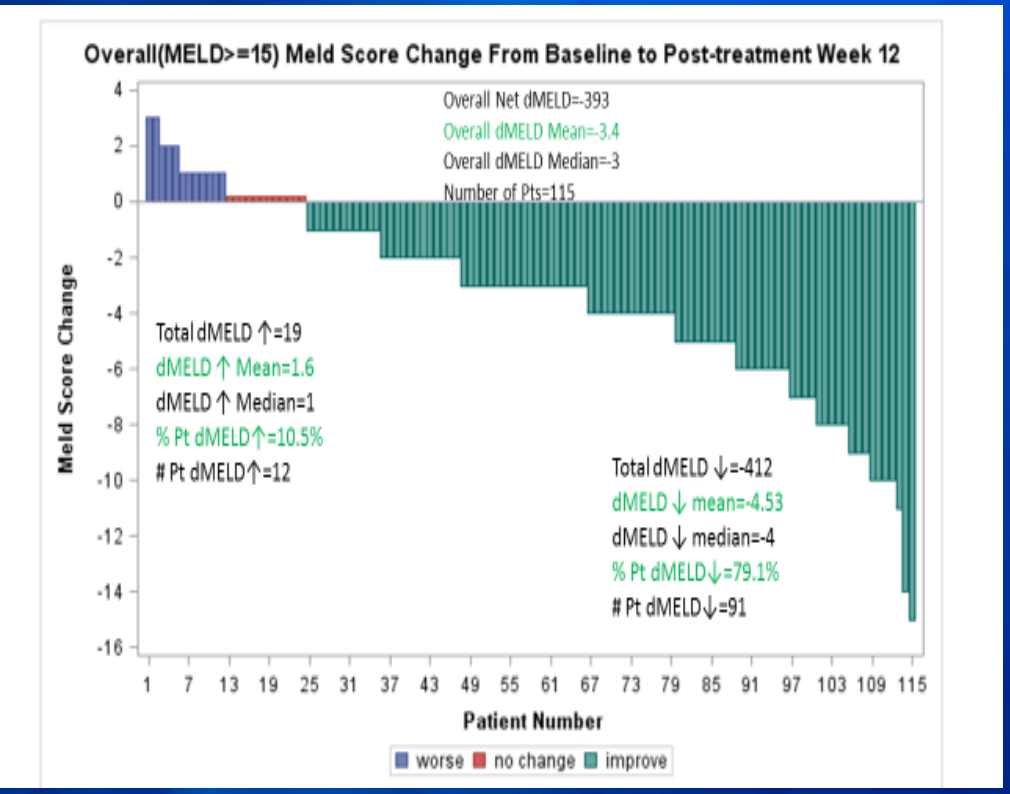




Schwarz JM, et al. ILC 2017; FRI-259

# MELD Score (MELD>=15) Change 12 WK Treated vs. Untreated UNOS Controls

**SOF Rx** **UNOS**




Dong et al., *Transplantation* 2017; in press

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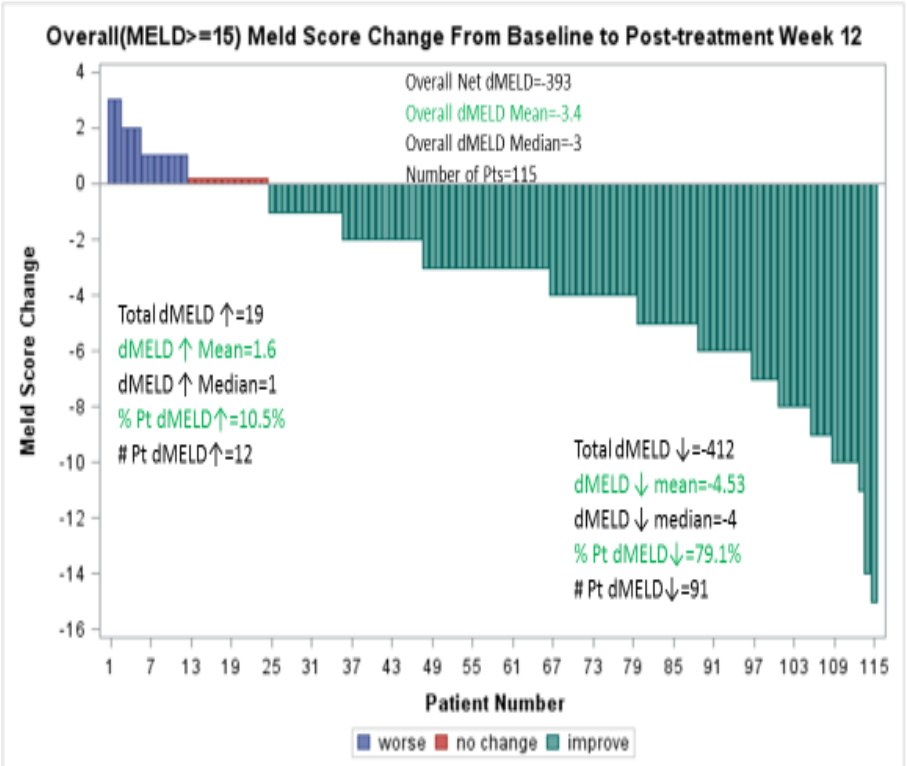
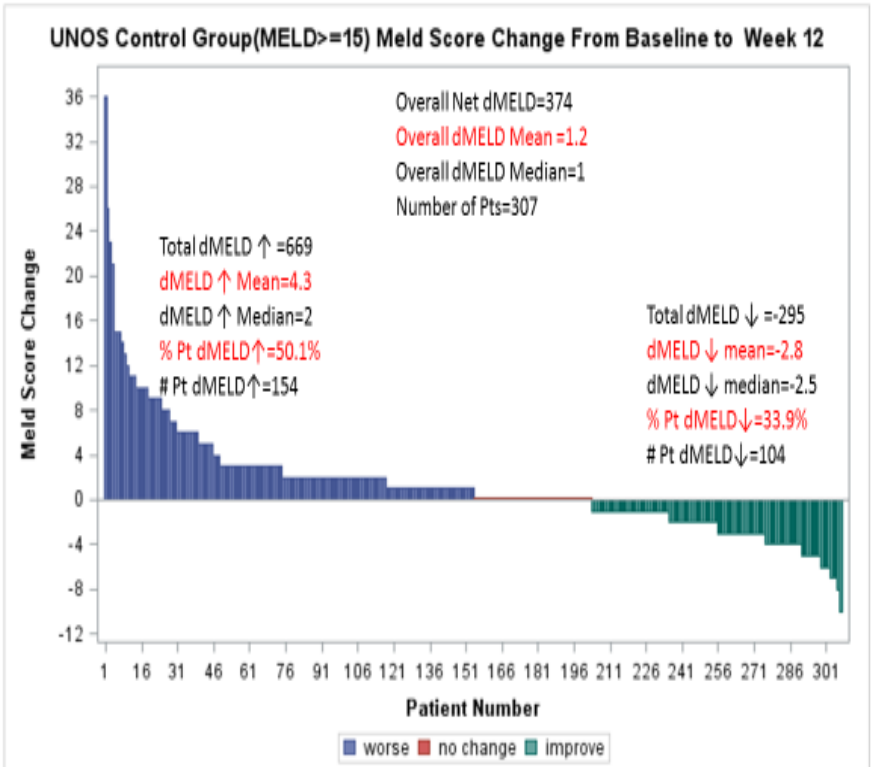



## UNOS




Dong et al., *Transplantation* 2017; in press

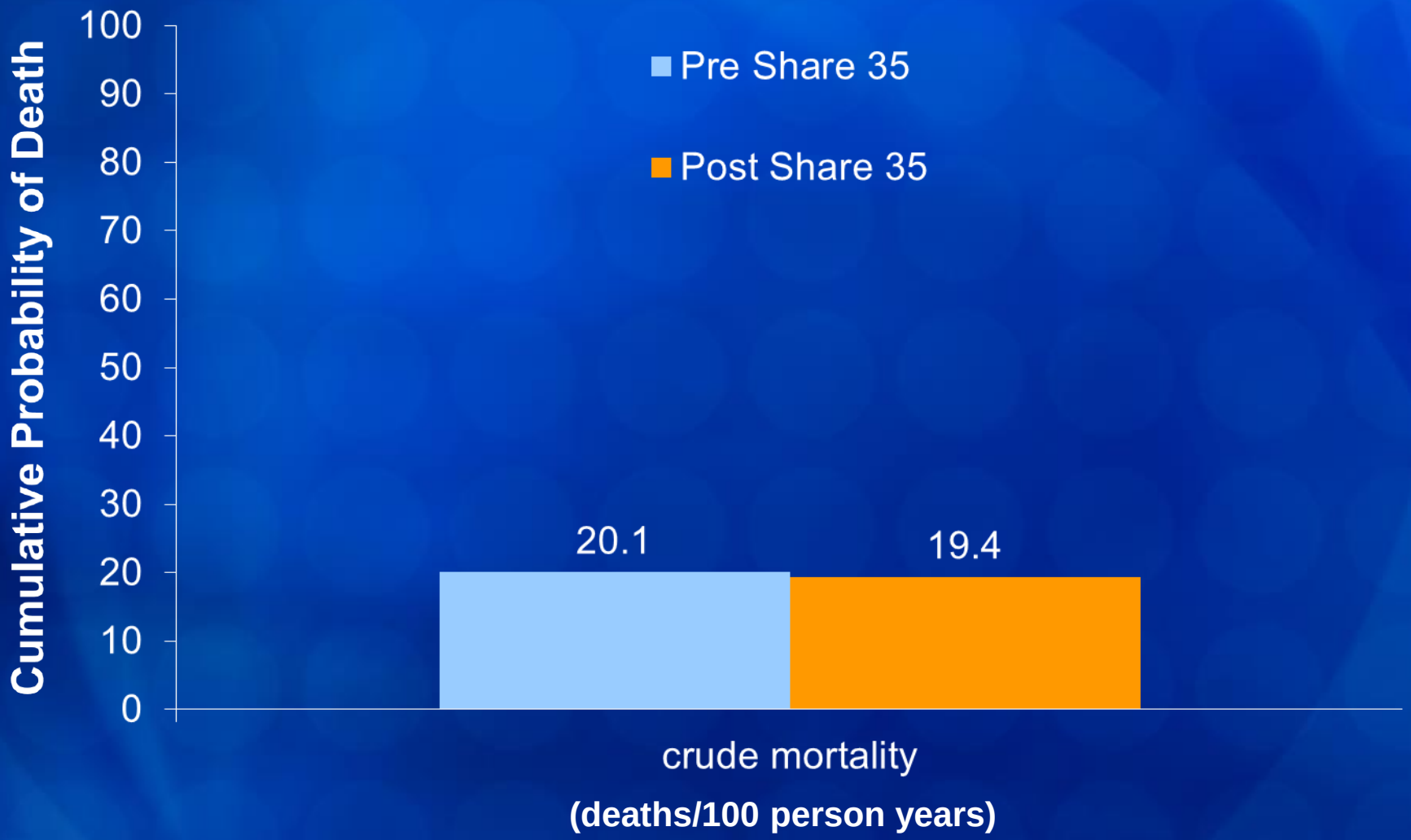
# Availability of HCV RNA pos Donors

- 4% more donors = 1 extra donor per 3

**What happens to the 85-90% of HCV +ve patients on the waitlist who did not get a HCV + donor?**

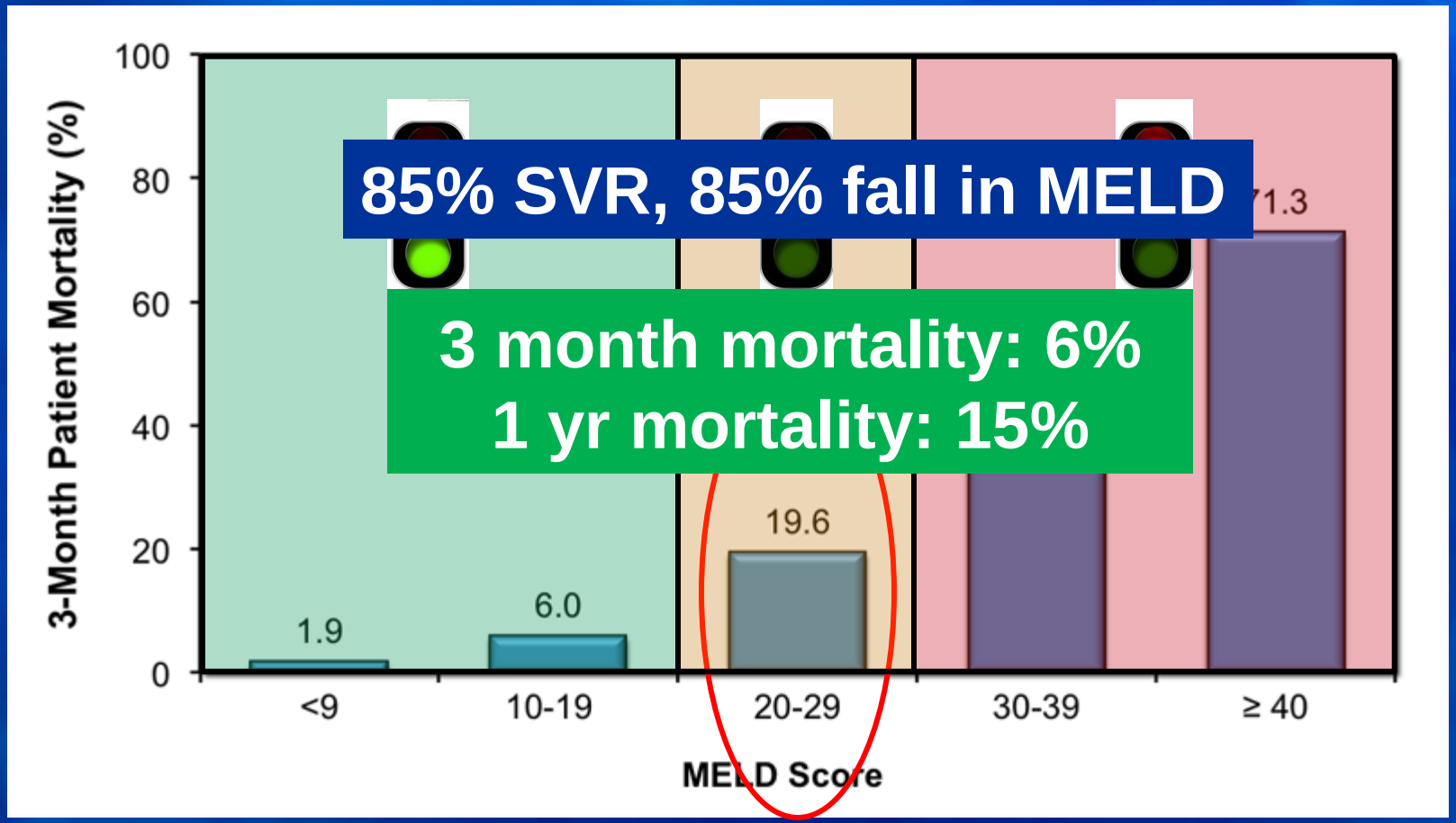
- 85-90% of HCV recipients would not undergo transplant in a more expeditious fashion.

# Waitlist Mortality – Risk of One Year on the Waitlist




Massie et al., *AJT* vol 15, issue 3: pages 659-667, 2015.

# Impact of Not Treating




*Hepatology*. 2001;33(2):464.

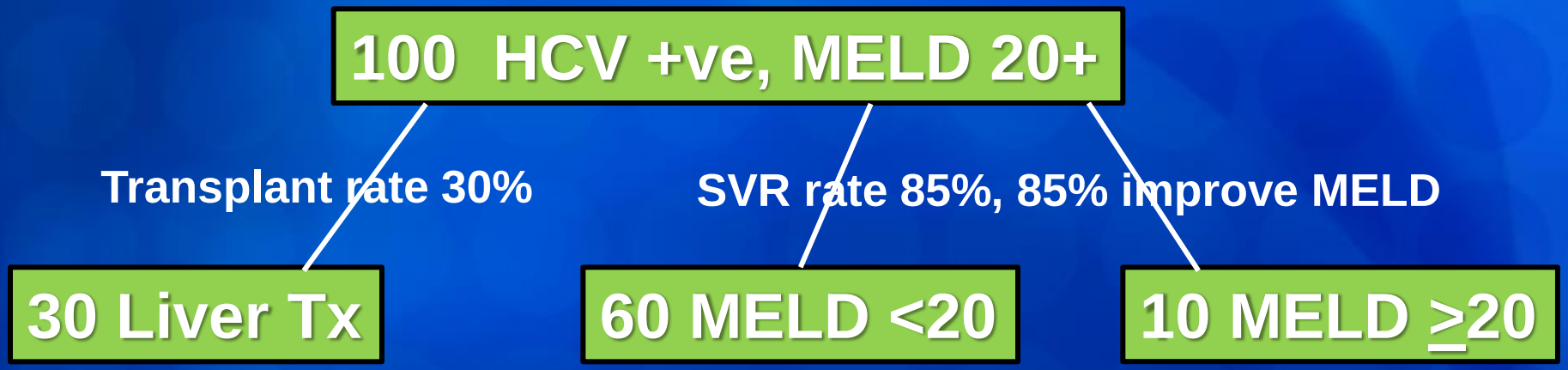
# Impact of Treating on Mortality

**100 HCV +ve, MELD 20+**

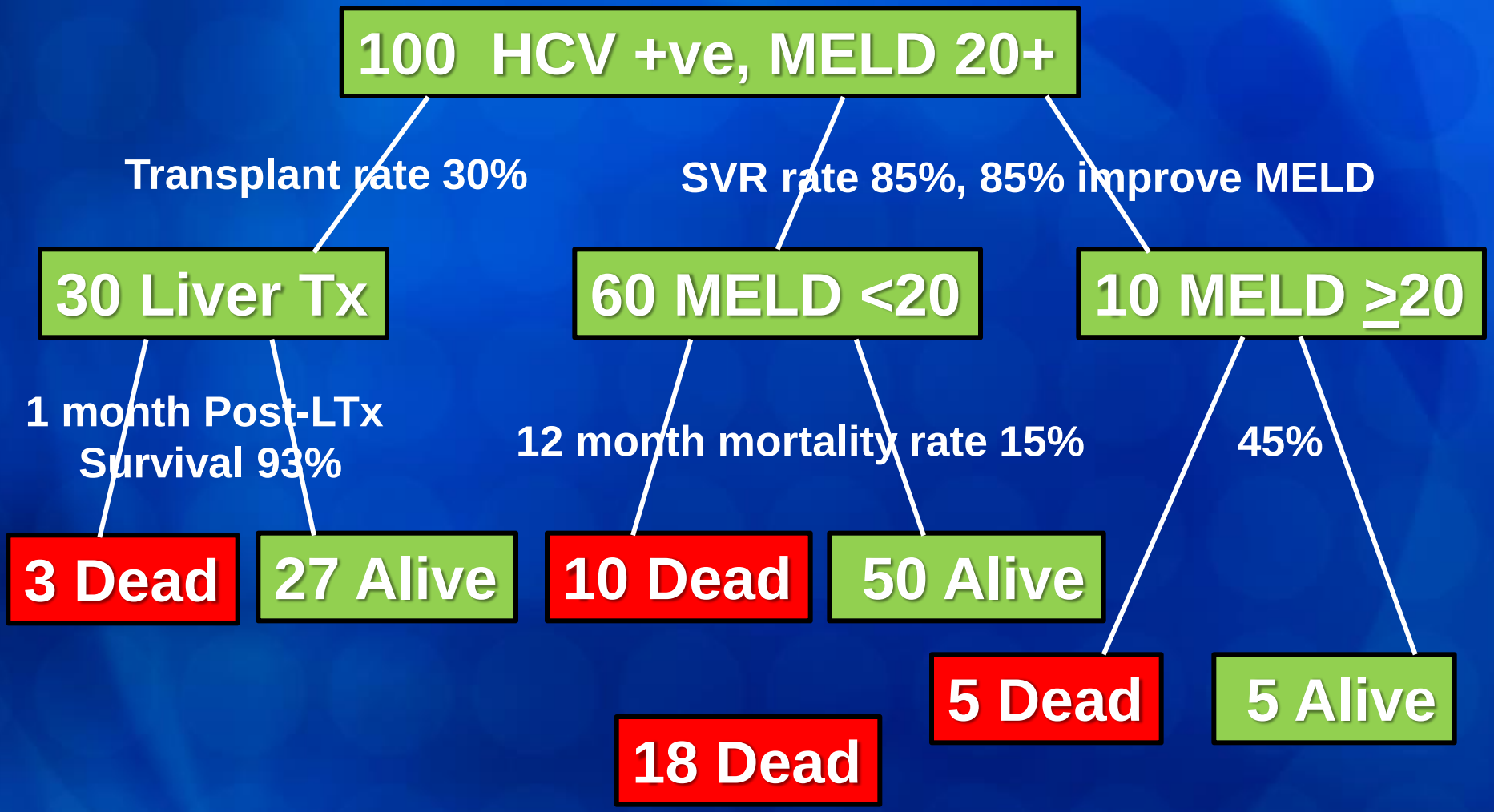
**Transplant rate 30%**

**SVR rate 95%, 85% improve MELD**

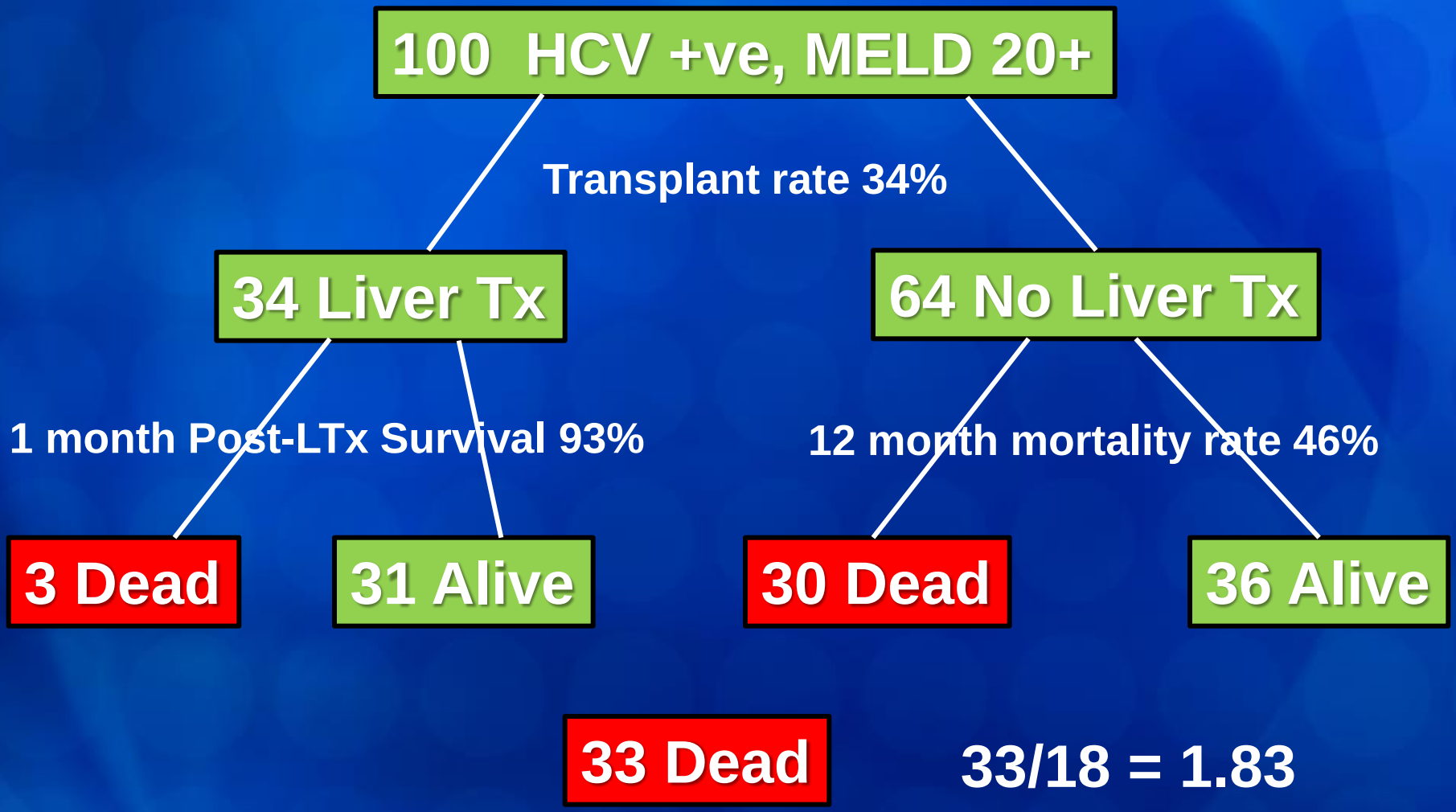
# Impact of Treating on Mortality



# Impact of Treating on Mortality

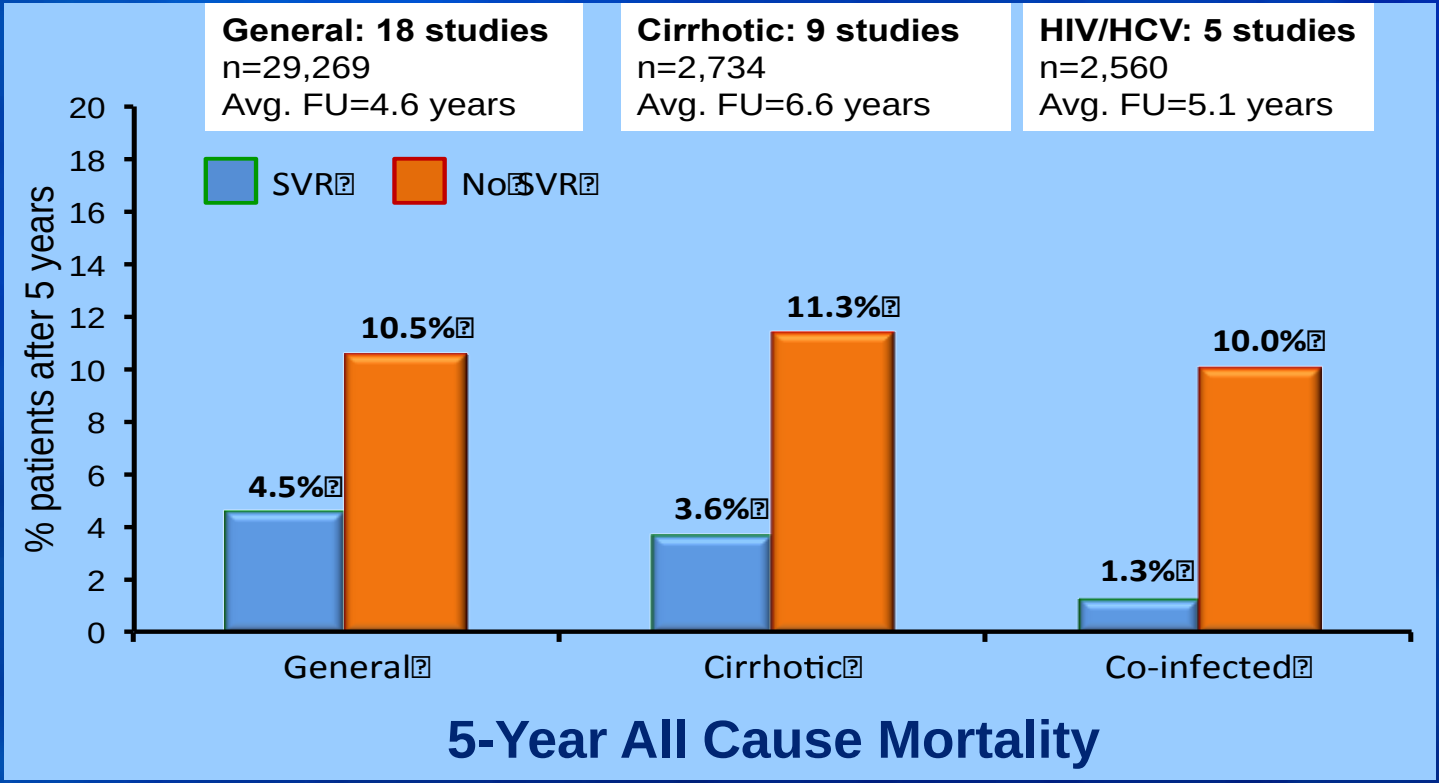


# Impact of Not Treating on Mortality



# Effects of SVR

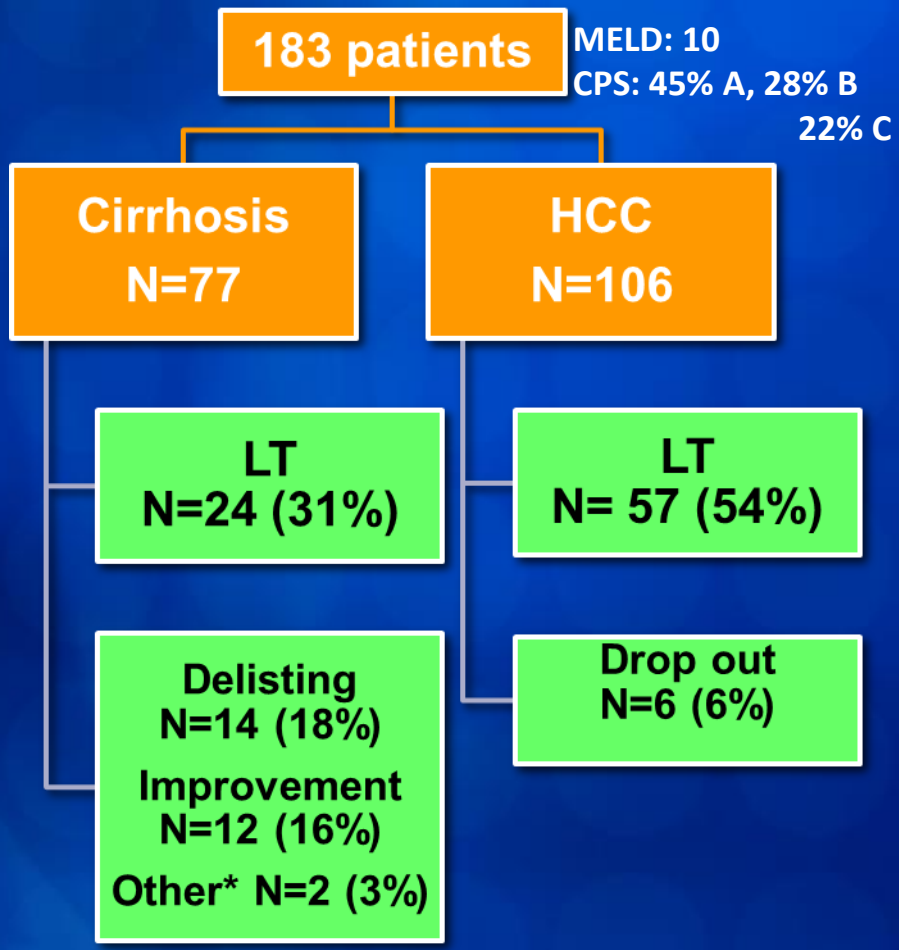
- Meta-analysis of 129 studies w/over 23,000 patients
- Estimated relative reductions in risk of liver transplant, HCC, all-cause mortality for SVR vs non-SVR after antiviral therapy
- RR substantially reduced for all groups with SVR




*Clin Infect Dis* 2015 Sep 1;61(5):730-40.

# DAA Therapy in HCV-Infected Patients on the Transplant Waiting List: Is Delisting Possible?

French multicenter cohort study

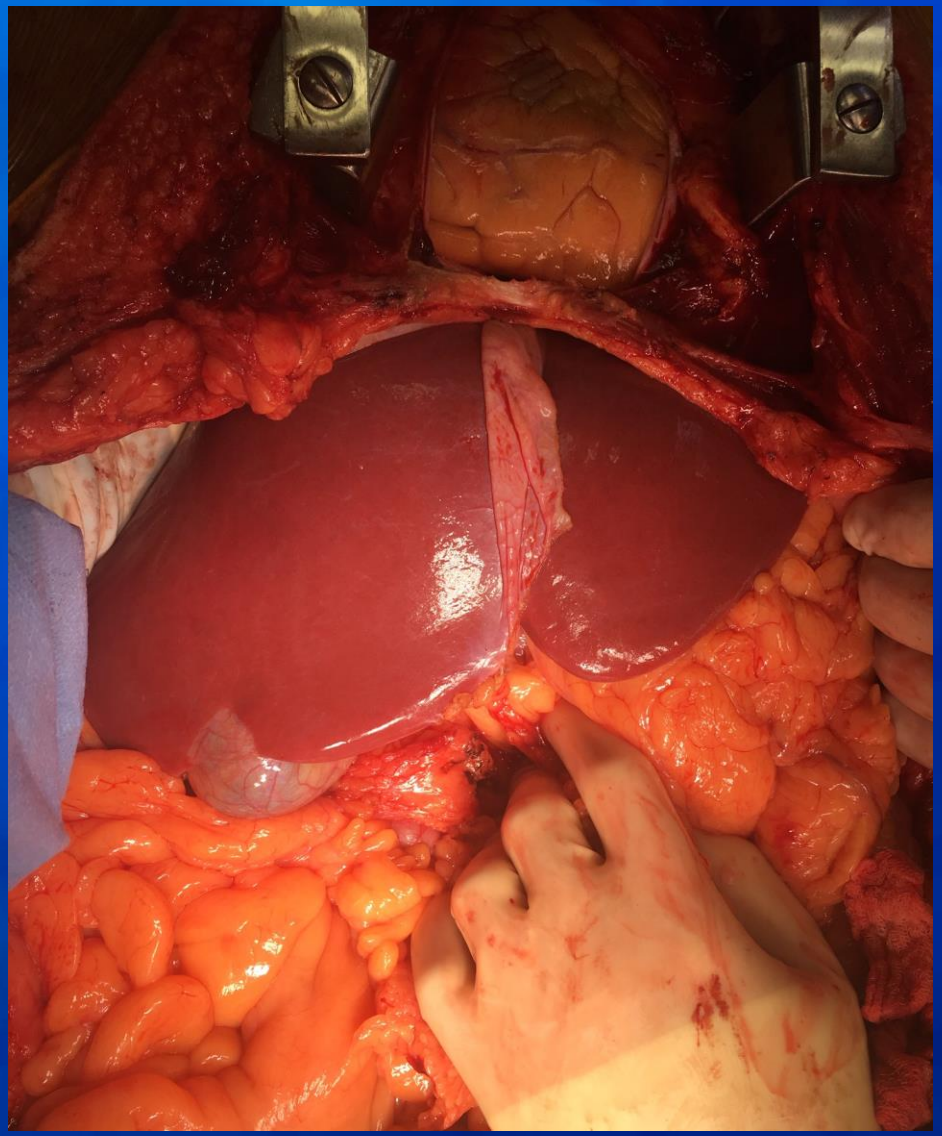



- 84% achieved SVR
- Complete clinical and biochemical response achieved in 36%

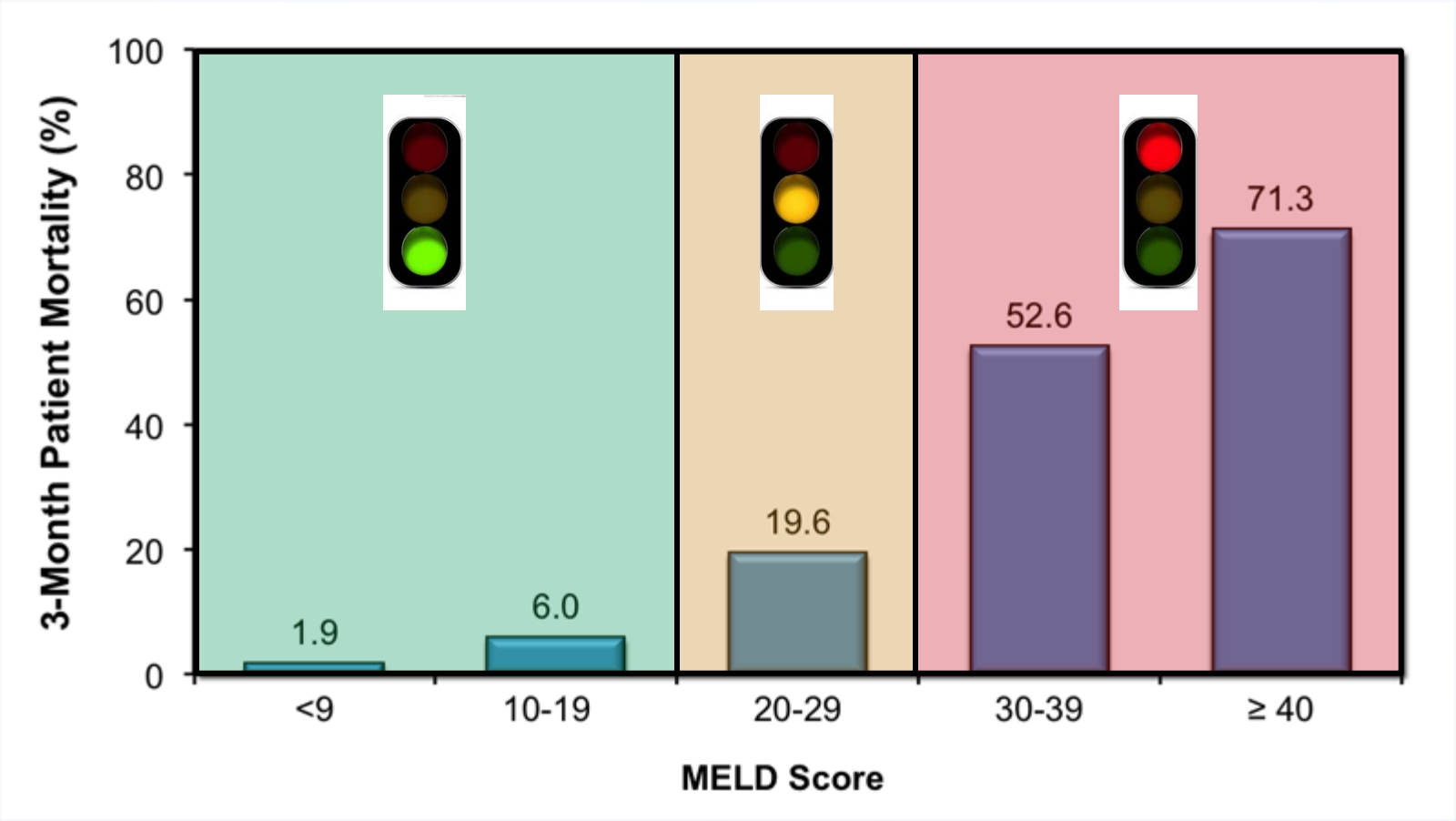
Mean follow-up: 68 wks (12-95)

Coilly A, *J Hep* 2016

# HCV Positive Donors

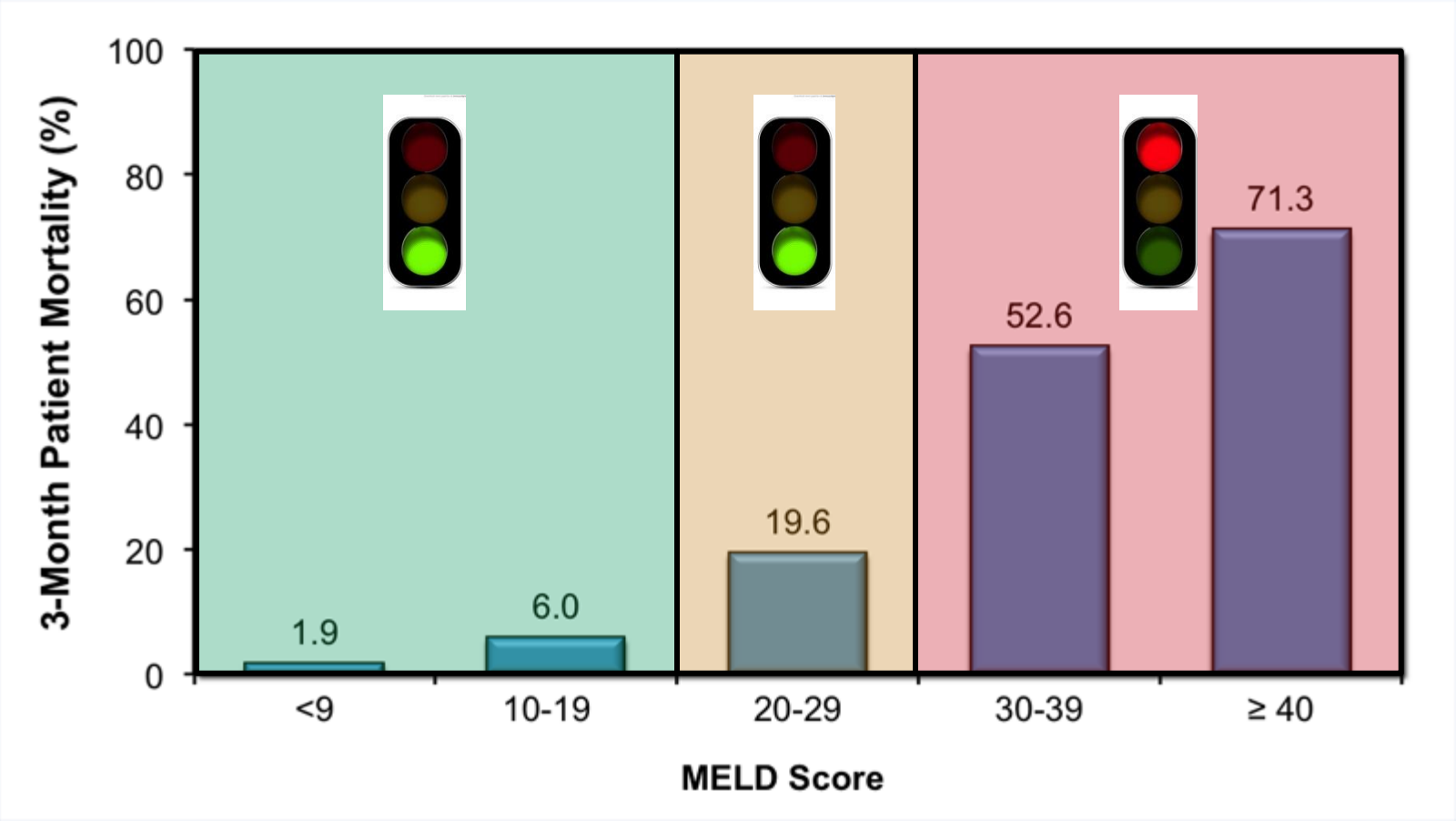


# Impact of Not Treating




*Hepatology*. 2001;33(2):464.

# Impact of Not Treating




*Hepatology*. 2001;33(2):464.

# Can I predict outcomes for an individual patient?

# Case

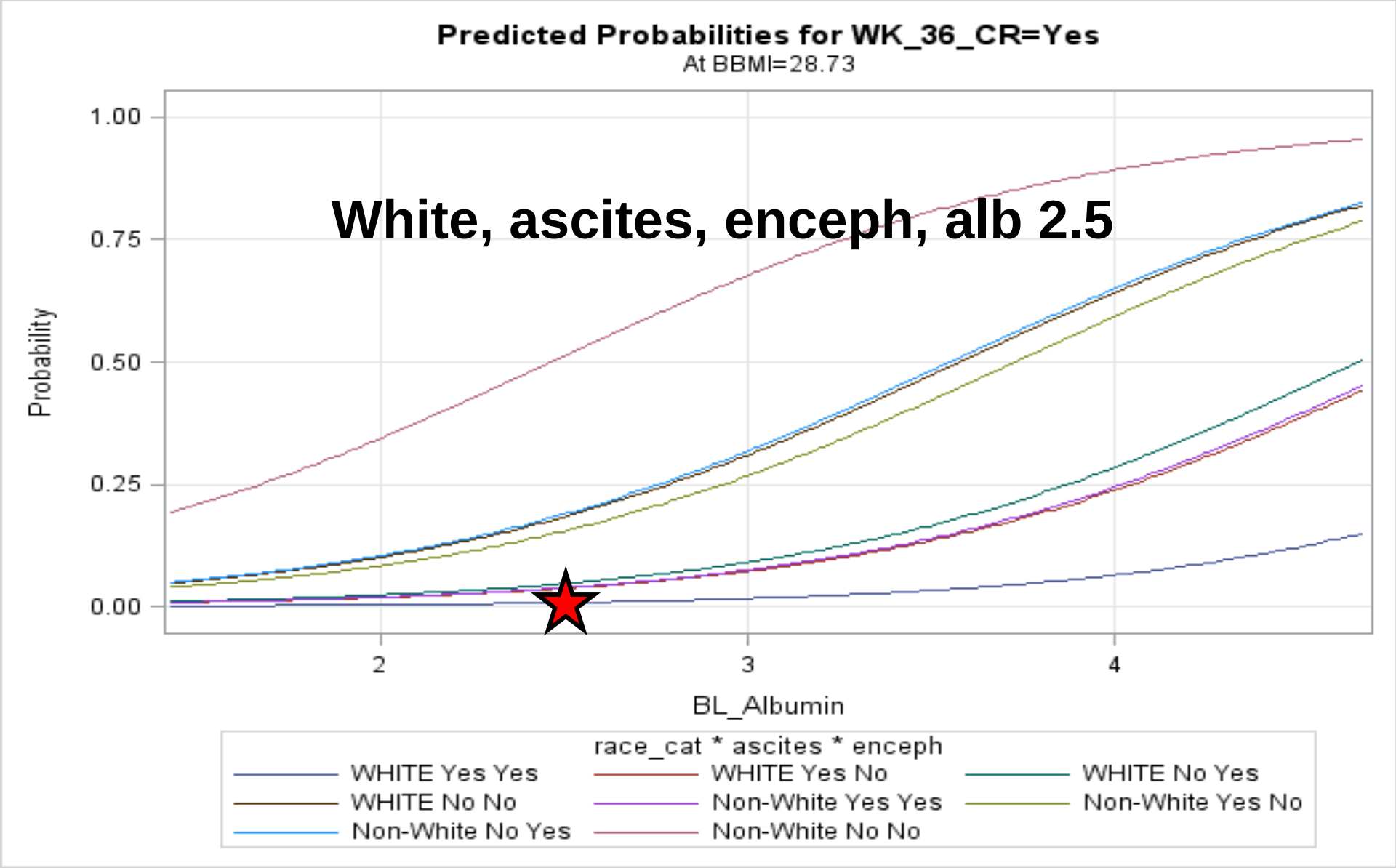
- 62 yr old man, white, Vietnam Vet
- HCV cirrhosis
- Mild ascites and encephalopathy
- MELD 25, albumin 2.8g/dl
- HCV relapse post IFN/RBV/TEL

## Logistic Regression Analysis for Complete Response (Yes vs None) Between Baseline and Week 36 (N=516)

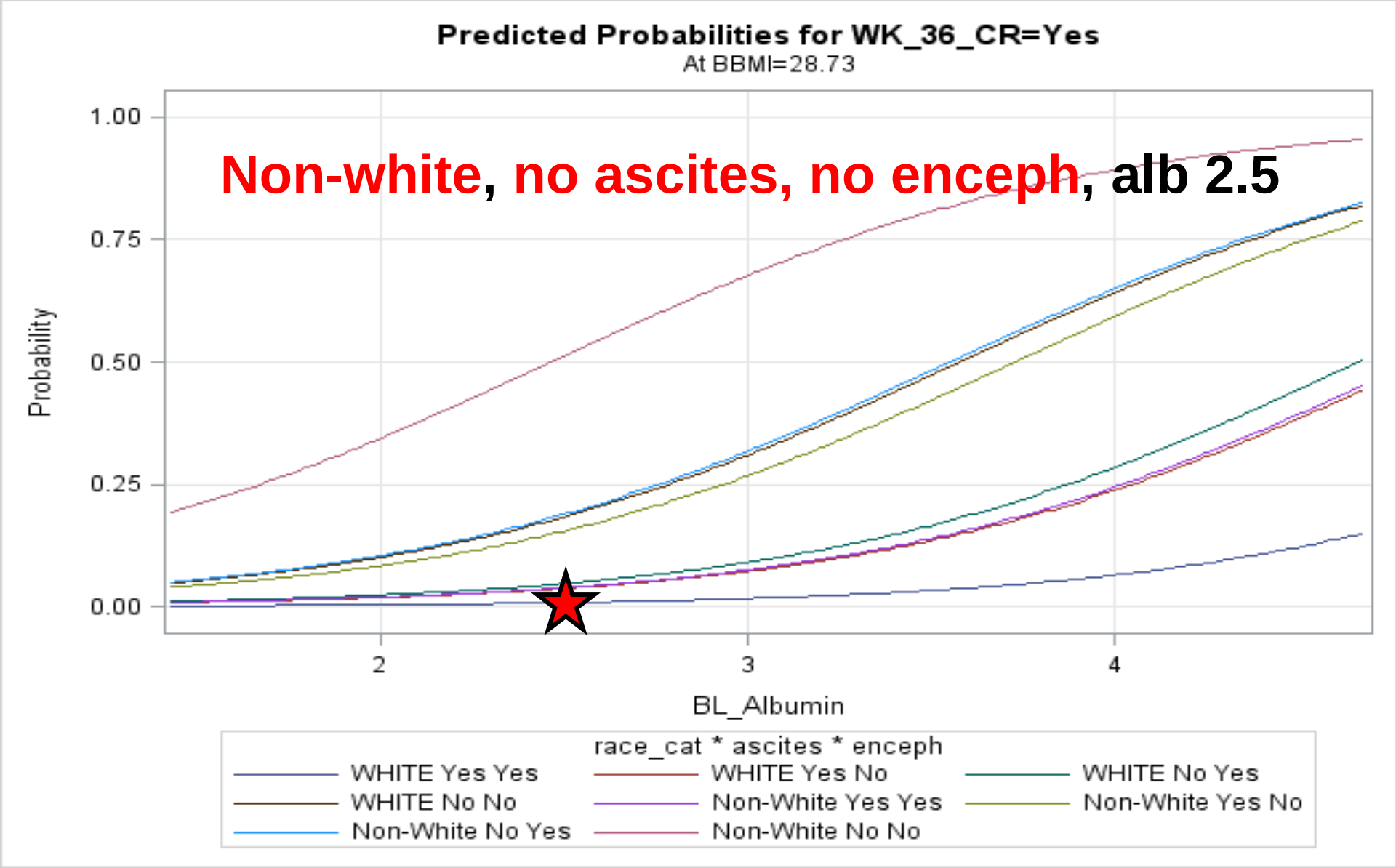
| Variable | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR(95% CL) | 2-Sided P-value | OR(95% CL) | 2-Sided P-value |
| Age group (Years): >=65 vs. <65 | 1.45 (0.69, 3.02) | 0.325 | | |
| Sex: Female vs. Male | 0.48 (0.24, 0.99) | 0.045 | | |
| Race: White vs. Non-White | 0.30 (0.14, 0.61) | 0.001 | 0.21 (0.09, 0.51) | 0.004 |
| Baseline BMI (>30) | 0.90 (0.84, 0.95) | 0.0007 | 0.91 (0.85, 0.98) | 0.009 |
| Baseline MELD Score: >=15 vs. <15 | 1.04 (0.53, 2.04) | 0.92 | | |
| Baseline Ascites: Yes vs. None | 0.20 (0.12, 0.36) | <0.0001 | 0.17 (0.09, 0.34) | <0.0001 |
| Baseline Encephalopathy: Yes vs. None | 0.22 (0.12, 0.41) | <0.0001 | 0.22 (0.11, 0.45) | <0.0001 |
| Baseline Albumin (<2.8g/dl) | 1.93 (1.09, 3.42) | 0.025 | 4.0 (1.92, 8.32) | 0.0002 |
| Baseline Platelets (10^3/uL): >=75 vs. <75 | 1.63 (0.90, 2.95) | 0.10 | | |

Complete response defined as:
normal INR + t bili + albumin,
with no ascites, no enceph

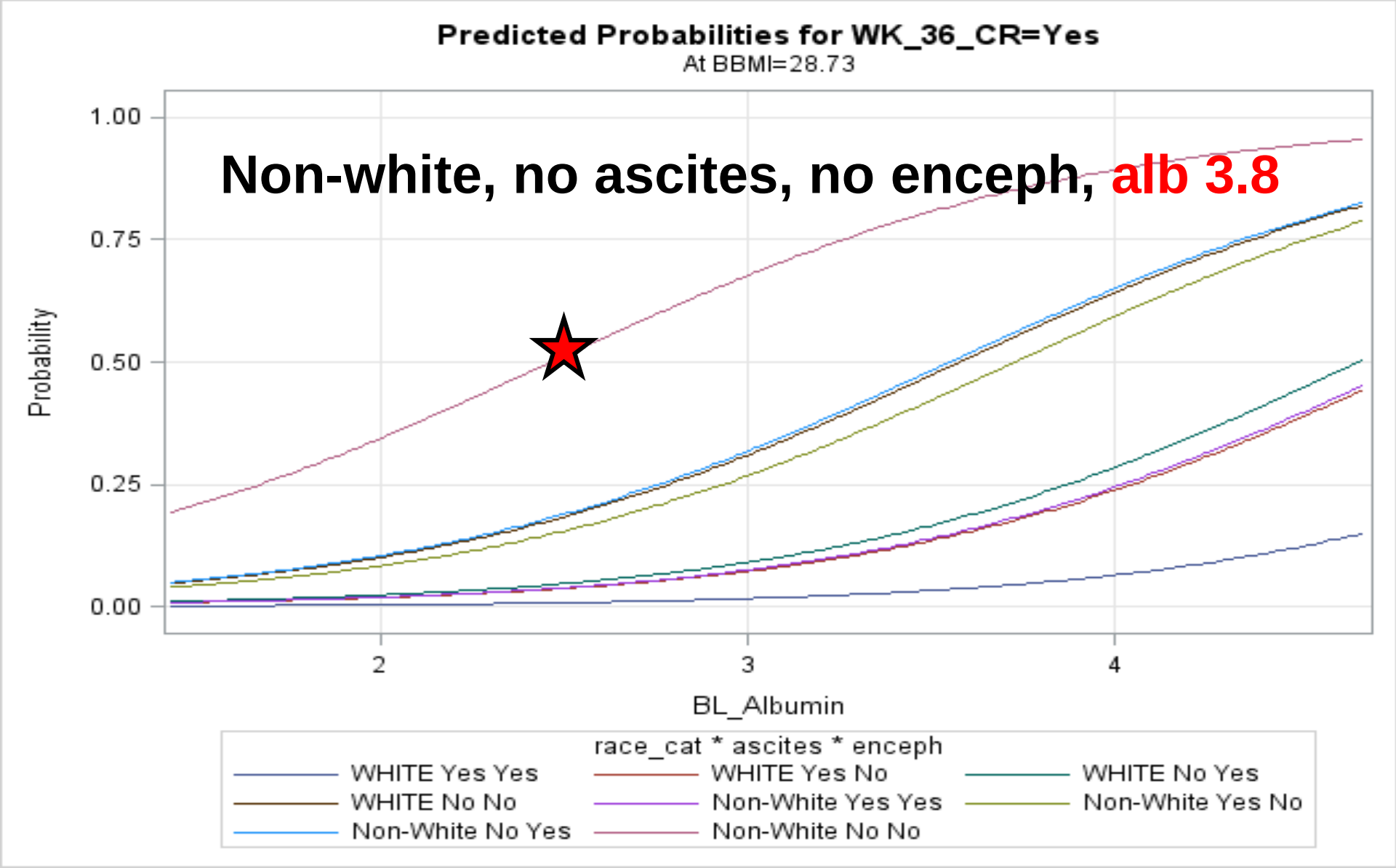
Dong et al., *Transplantation* 2017; in press



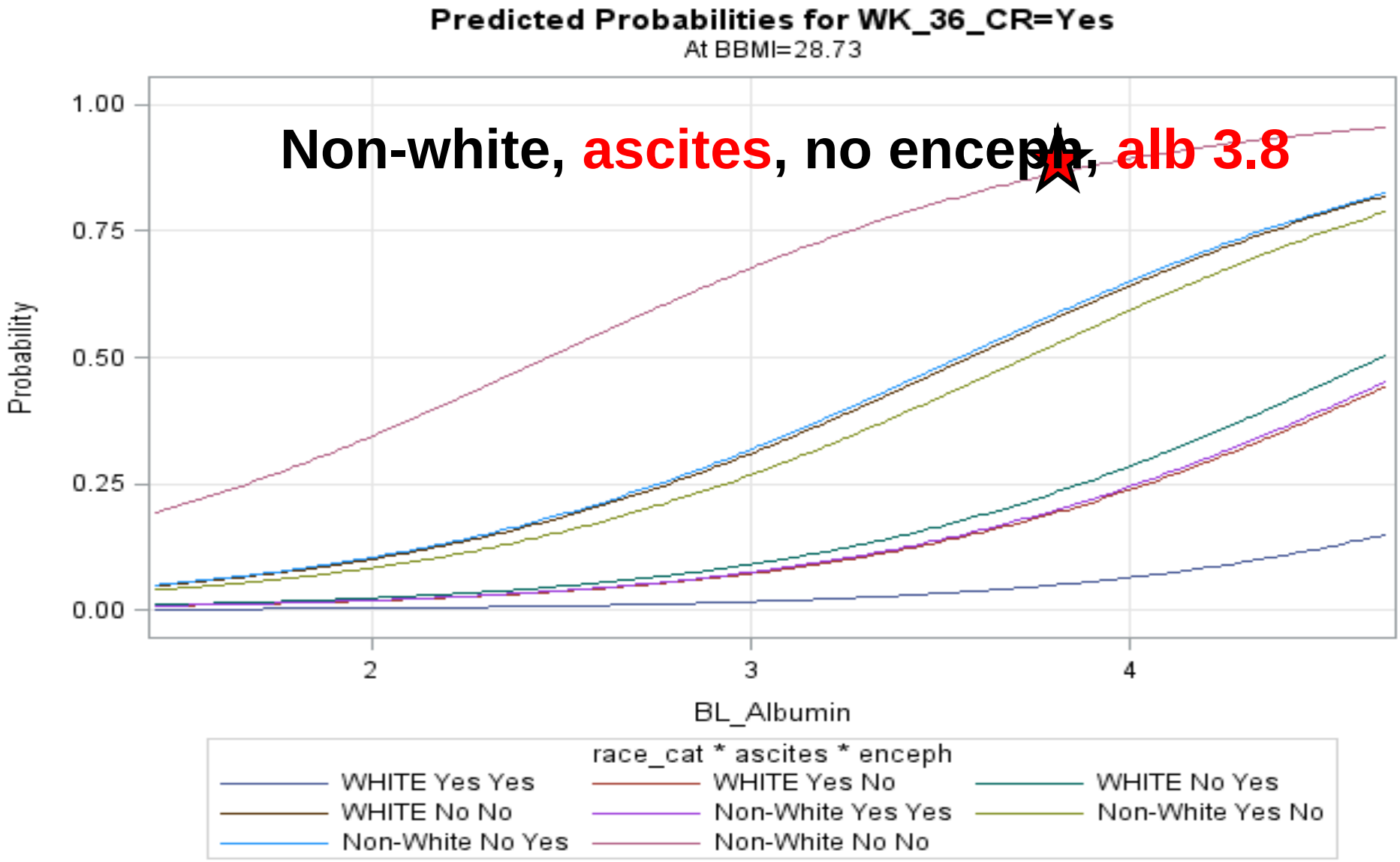

Dong et al., *Transplantation* 2017; in press




Dong et al., *Transplantation* 2017; in press




Dong et al., *Transplantation* 2017; in press




Dong et al., *Transplantation* 2017; in press

# Waitlist Jeopardy!

| HODGEPODGE | 10 OR MORE LETTER WORDS | BRITANNICA ENCYCLOPEDIA | Deceased Donors | GIVE ME A "H" | 2009 FAMOUS NEWS |
|---|---|---|---|---|---|
| $200 | $200 | $200 | $200 | $200 | $200 |
| $400 | | $400 | $400 | $400 | $400 |
| $600 | $600 | $600 | $600 | $600 | $600 |
| $800 | $800 | $800 | $800 | $800 | $800 |
| $1000 | $1000 | $1000 | $1000 | $1000 | $1000 |

# Deceased donor, 28 yrs old, NYC resident, male, s/p MVA

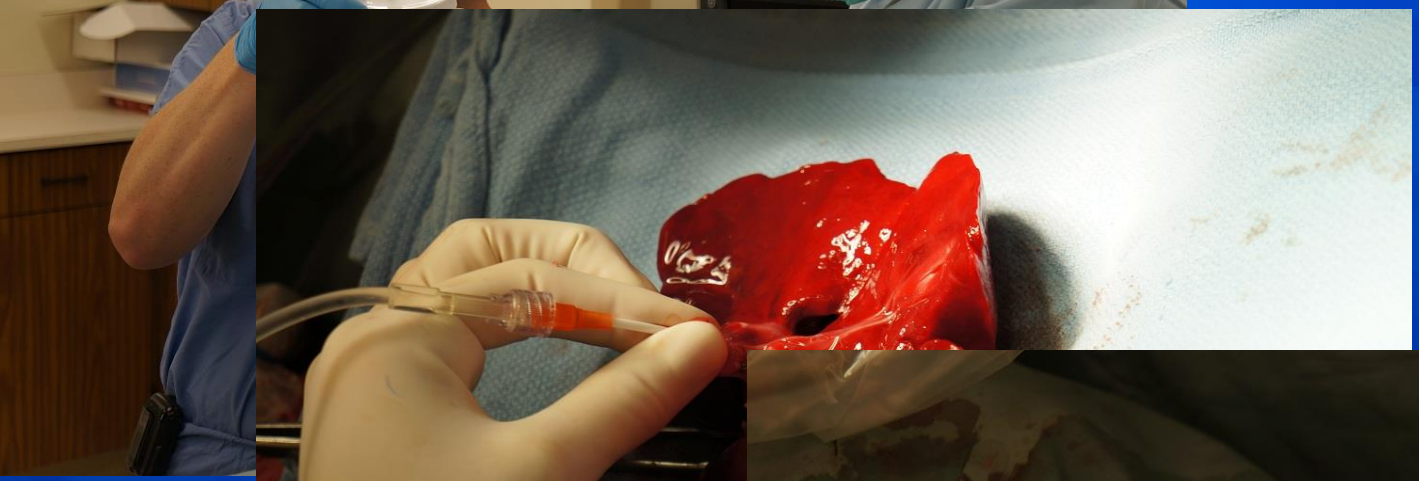
- 45 yr old mother of two teenage children, Brooklyn resident
- HCV, MELD score 34, type 1 HRS
- Socially intact, supportive family
- Jaundice, ascites, SBP, encephalopathy

- 72 yr old man, Vietnam Veteran, New Jersey resident
- HCV, HCC, Milan criteria (2.2cm)
- Exception MELD score 34, lab MELD 11
- Socially intact

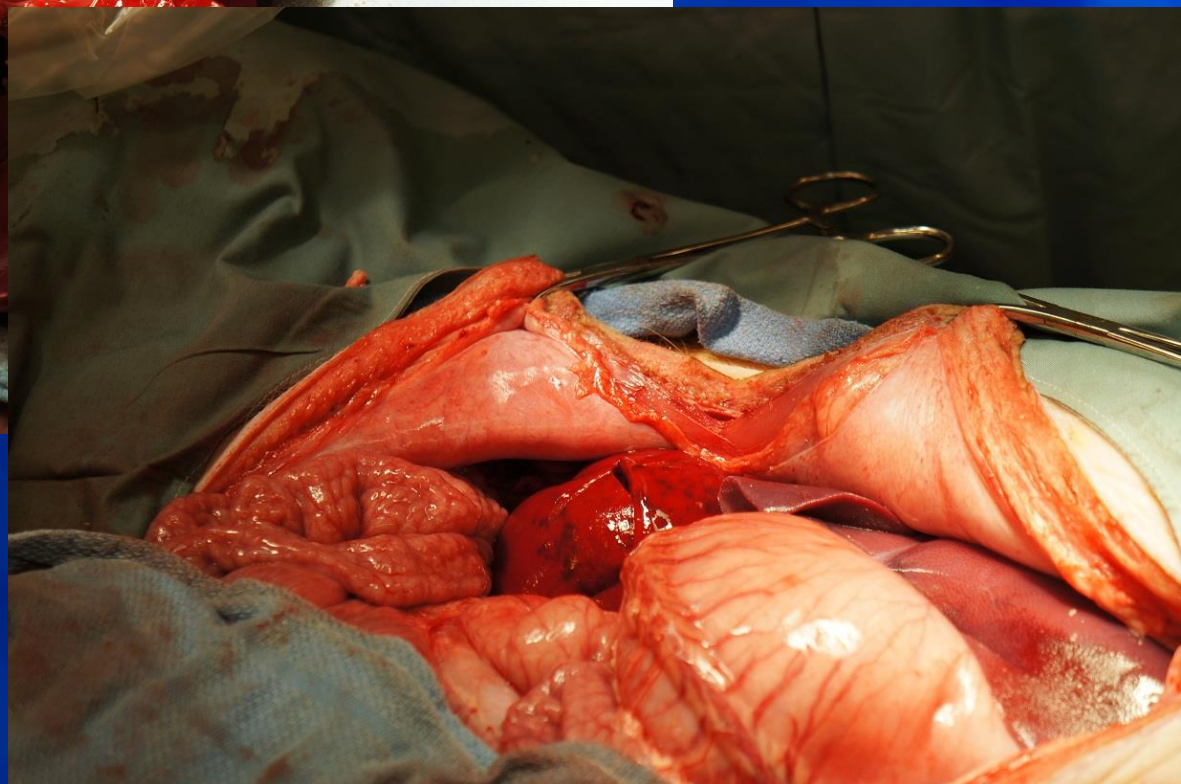
# Deceased donor, 28 yrs old, NYC resident, male, s/p MVA

- 45 yr old mother of two teenage children, Brooklyn resident
- Alcoholic hepatitis, MELD score 34
- Socially intact, supportive family
- Jaundice, ascites, SBP, encephalopathy
- Last drink 1 month ago

- 72 yr old man, Vietnam Veteran, New Jersey resident
- HCV, HCC, Milan criteria (2.2 cm)
- Exception MELD score 34, lab MELD 11
- Socially intact







# Who should get the organ now?

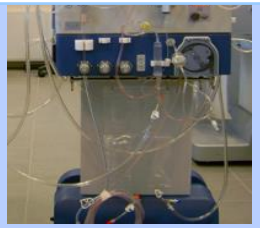
# Bioarticficial Liver: From Bench to Bedside

## RALF Study: Reversible Ambulatory Liver Failure

**Prototype Mayo SRBAL "The Cart"**

**Generation #1**

**Large Animal Testing**



**Mayo SRBAL Clinical Use**


MAYO
CLINIC

# RALF Study:
# Reversible Ambulatory Liver Failure

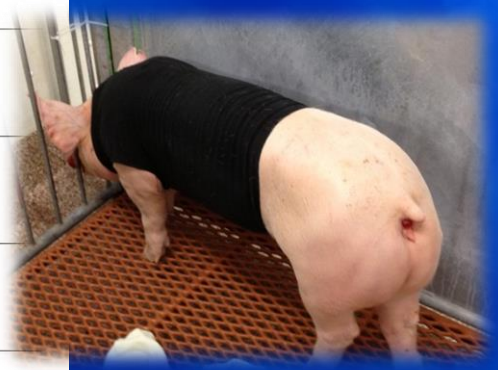
- Continuous perfusion (250mL/min)

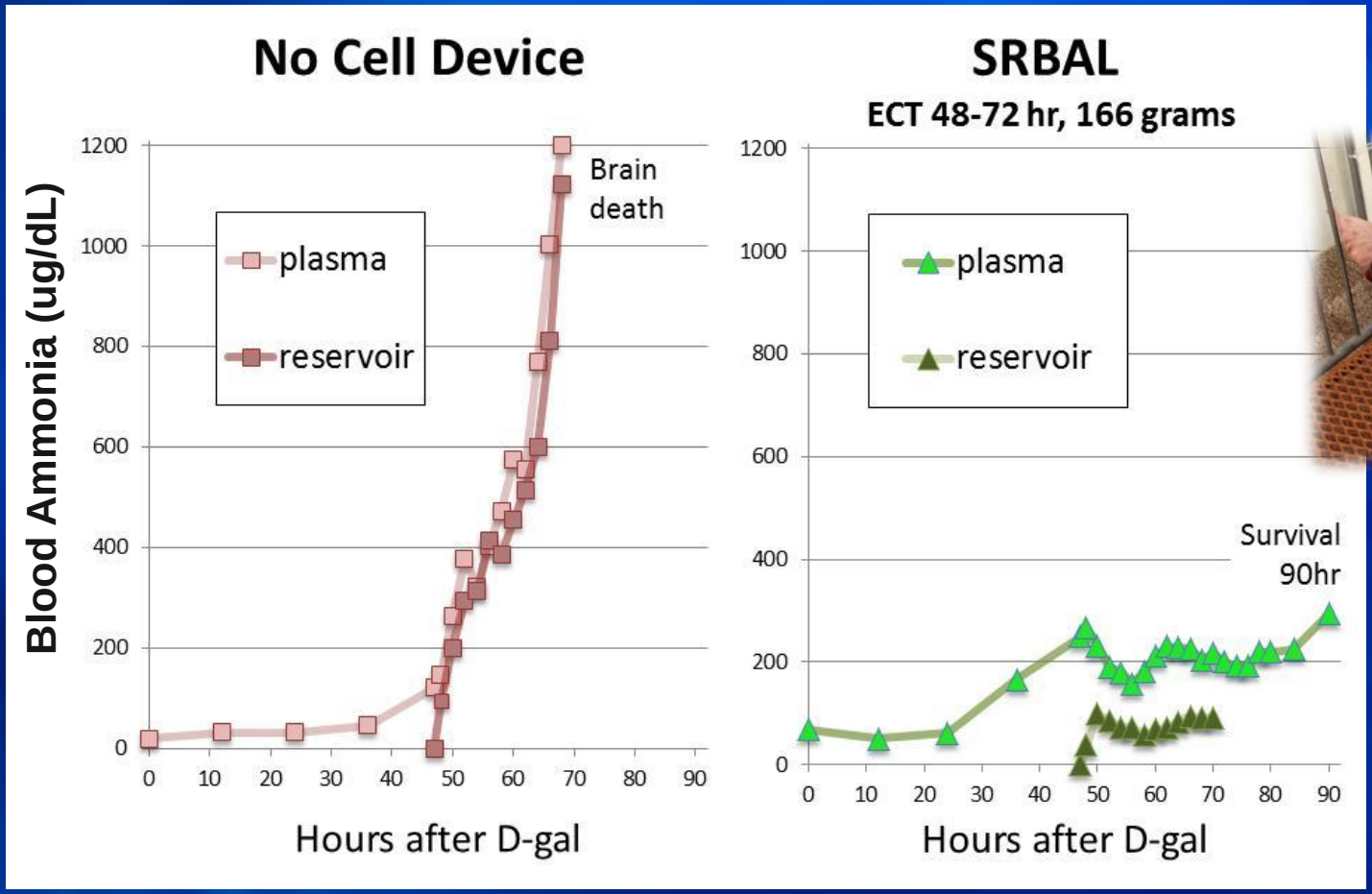
- 250g (~25%)

RALF Study:

# Ammonia Detoxification: No Cell vs SRBAL Device

ALF pig – ambulatory at 90 hrs after 24hr SRBAL treatment





# RALF Study:
# Reversible Ambulatory Liver Failure

Journal of Hepatology **2015** vol. 63 | 388–398

Research Article

CrossMark

EASL | JOURNAL OF HEPATOLOGY

## Pivotal preclinical trial of the spheroid reservoir bioartificial liver

Jaime M. Glorioso[1], Shennen A. Mao[1], Brian Rodysill[1], Taufic Mounajjed[2], Walter K. Kremers[3,4], Faysal Elgilani[4], Raymond D. Hickey[4,5], Hakon Haugaa[6,7], Christopher F. Rose[8], Bruce Amiot[9], Scott L. Nyberg[1,4,*]

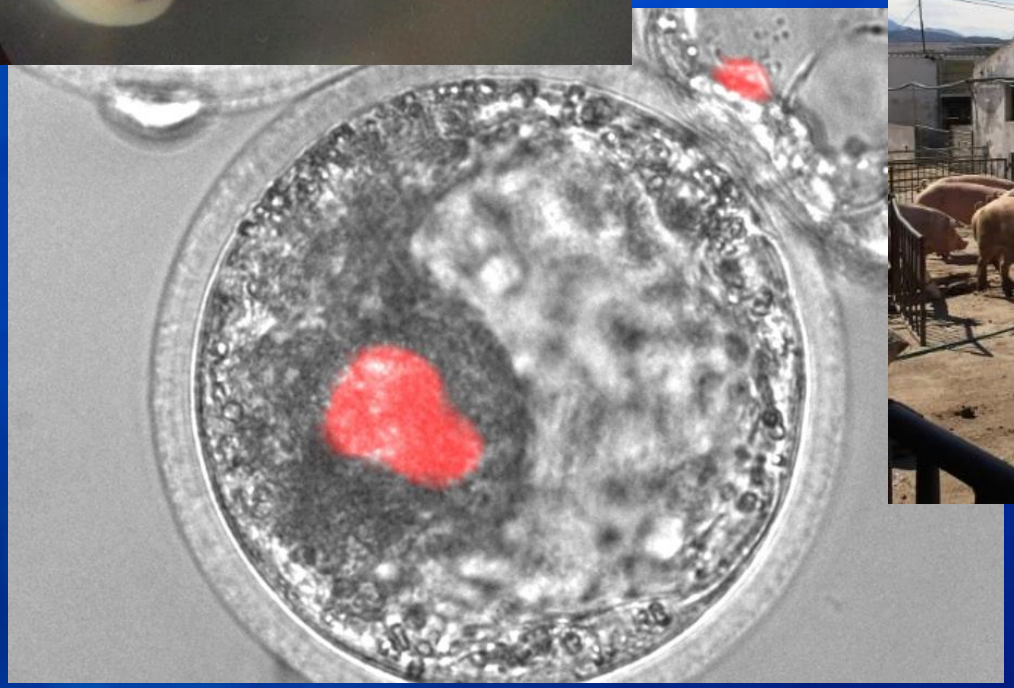
[1]*Department of Surgery, Mayo Clinic, Rochester, MN, USA;* [2]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA;* [3]*Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA;* [4]*William J. von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN, USA;* [5]*Department of Molecular Medicine, Mayo Clinic, Rochester, MN, USA;* [6]*Department of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway;* [7]*Institute of Clinical Medicine, University of Oslo, Norway;* [8]*Hepato-Neuro Laboratory, CRCHUM, Universite de Montreal, Quebec, Canada;* [9]*Brami Biomedical, Inc., Minneapolis, MN, USA*

See Editorial, pages 303–305

# What's next?

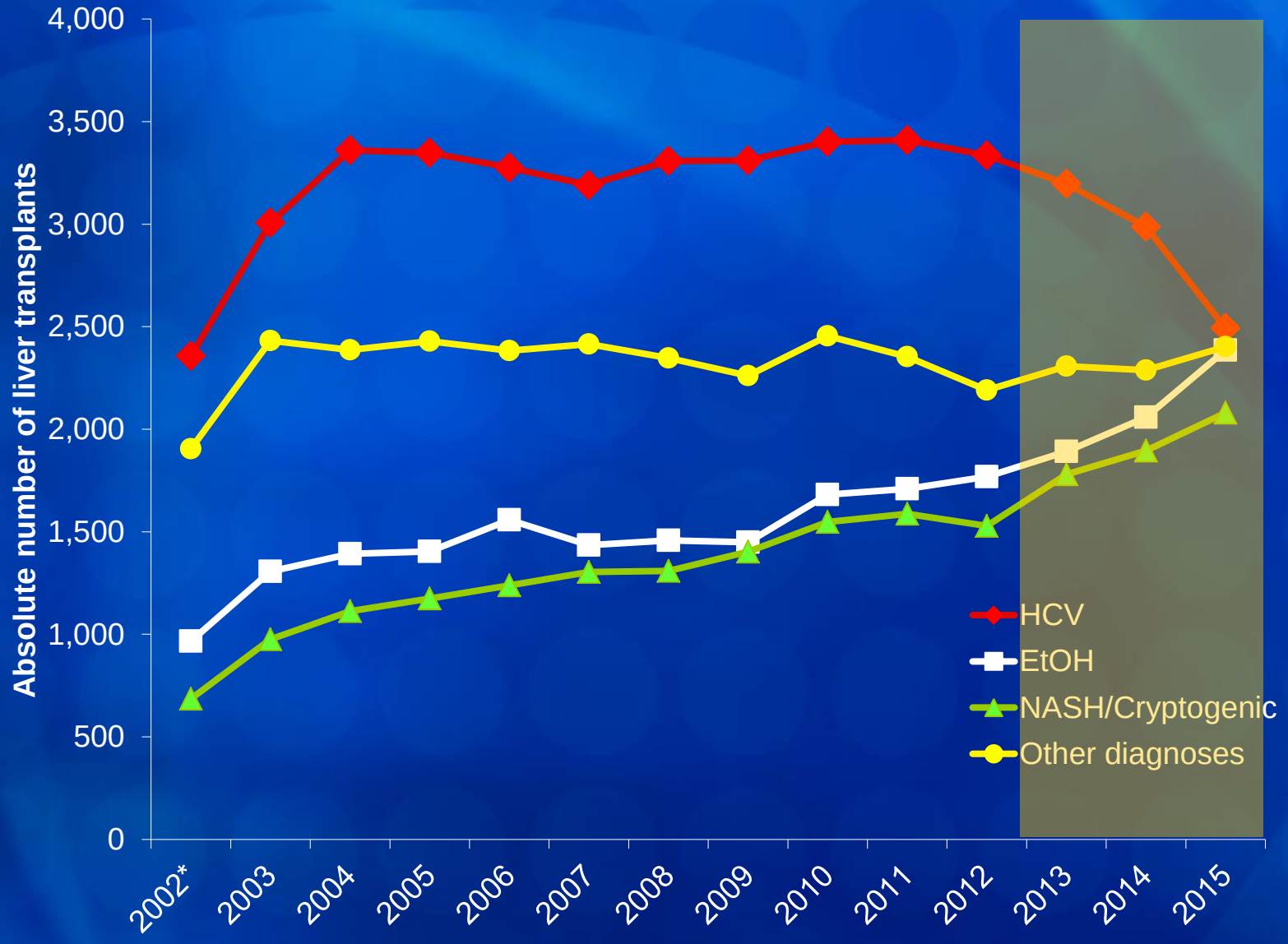
Wu ei al., *Cell*, 2017, Vol 168: 3: 473-486

# What's next?



Wu ei al., *Cell*, 2017, Vol 168: 3: 473-486

# Indications for Waitlisting for liver transplantation




**Goldberg et al., *Gastroenterology* 2017.**

# Conclusions

- HCV treatment should be considered in patients with decompensated liver disease with MELD scores </=30
- Treatment should be with SOF + LDV/VEL/DCV + RBV x 12 wks or SOF + LDV/VEL/DCV x 24 wks
- Decisions to treat should be individualized.

# Thank you!

HIV Management
Hepatitis Management

# THE NEW YORK COURSE