APASL 2013 SINGAPORE

APASL Liver Week

6th - 10th June 2013

Suntec Singapore • Singapore

Transforming Science to Clinical Practice

"How do you optimize HCV Treatment for Cirrhotic Patients"

APASL STC Cebu

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Disclosures

- Advisory Board
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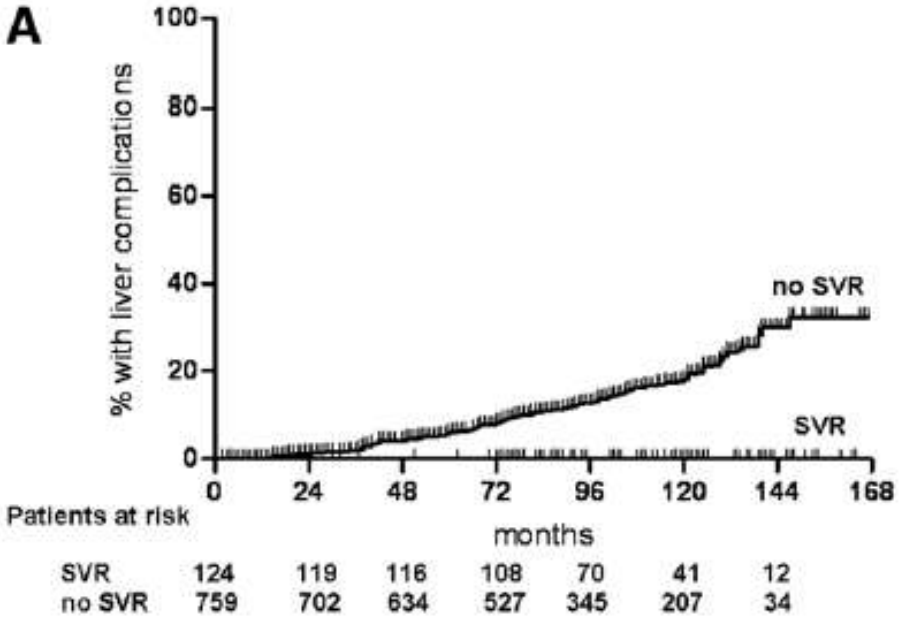
  - Bristol Myer Squibb
  - MSD
  - Roche
  - Boehinger Ingelheim

Overview

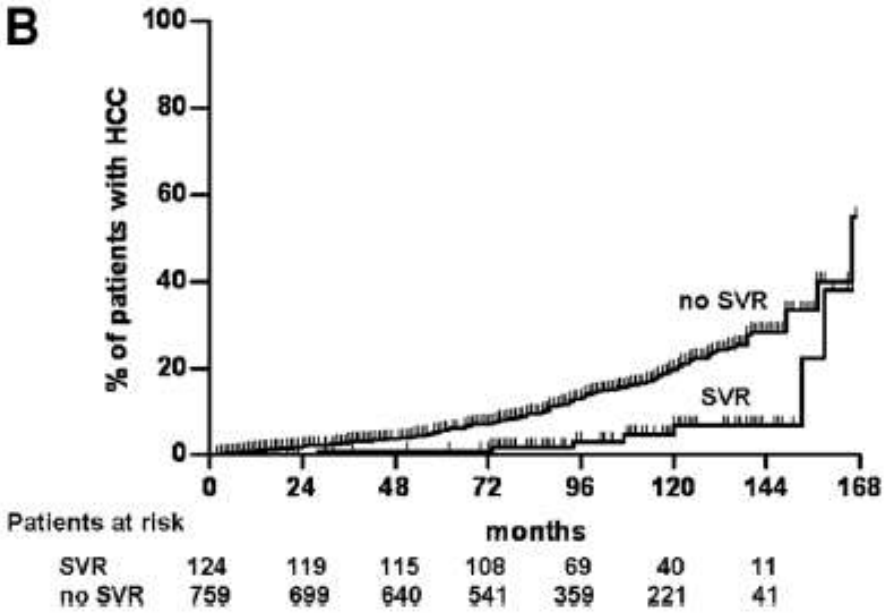
- Preamble
- Standard of Care: PR in Asians vs Caucasians
- Predictors of SVR and RVR
- Treatment failures
- DAA in cirrhosis
- Decompensated cirrhosis

Treatment of HCV Cirrhosis Prevents Liver Disease Endpoints

Reduction in Liver Decompensation

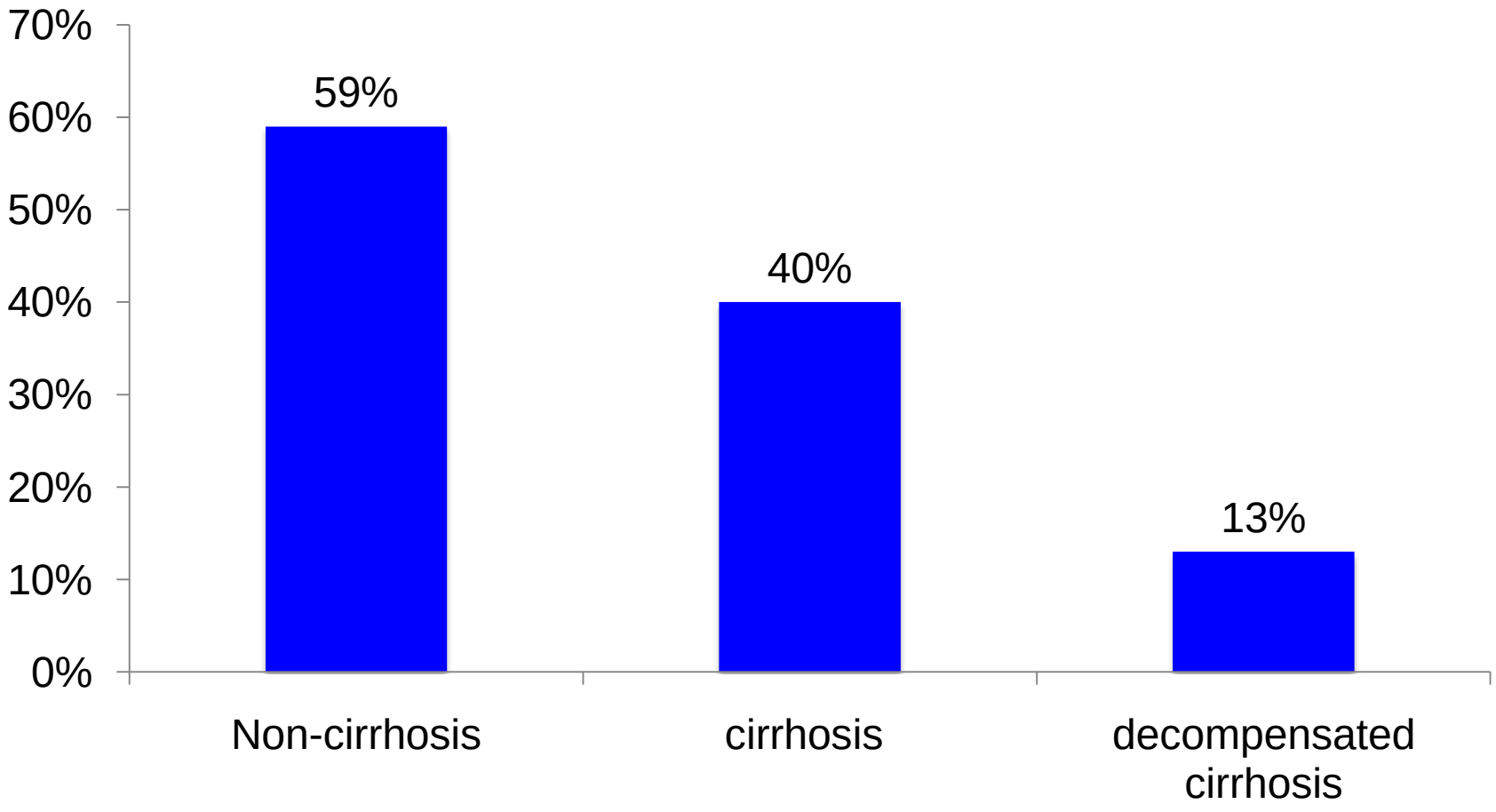


Reduction in HCC



Bruno Hepatology 2007

SVR declines with progressive liver disease on PEG-Rib



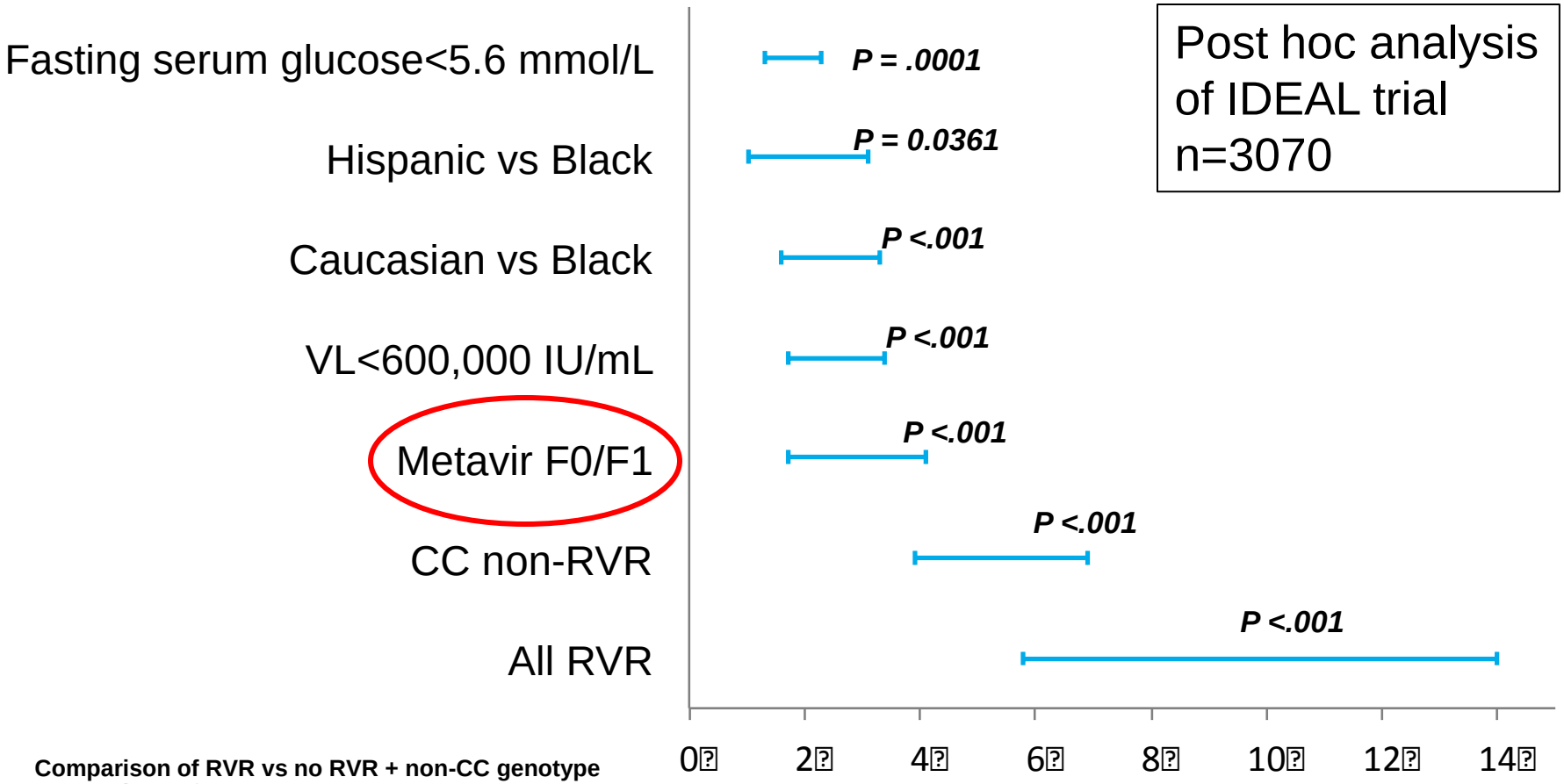
Stattemayer, Clin Gastro Hepatol 2011;9:344–350
Everson GT, et al. Hepatology. 2005;42:255-262.

Adverse Events in HCV Treatment Groups

Adverse effect / Treatment discontinuation	Non-Cirrhotics	Compensated Cirrhotics	Decompensated Cirrhotics
Fatigue	55%	34%	59%
Headache	50%	54%	45%
Impaired concentration	17%	6%	2%
Infection	2%	0%	4%
Anaemia	15%	35%	50%
Neutropaenia	6%	38%	53%
Thrombocytopaenia	17%	24%	50%
Dose reductions	27%	30%	42%
Discontinuation	13%	12%	20%

Predictors of SVR and RVR

RVR is Stronger than All Baseline Predictors of SVR Using Peginterferon/Ribavirin

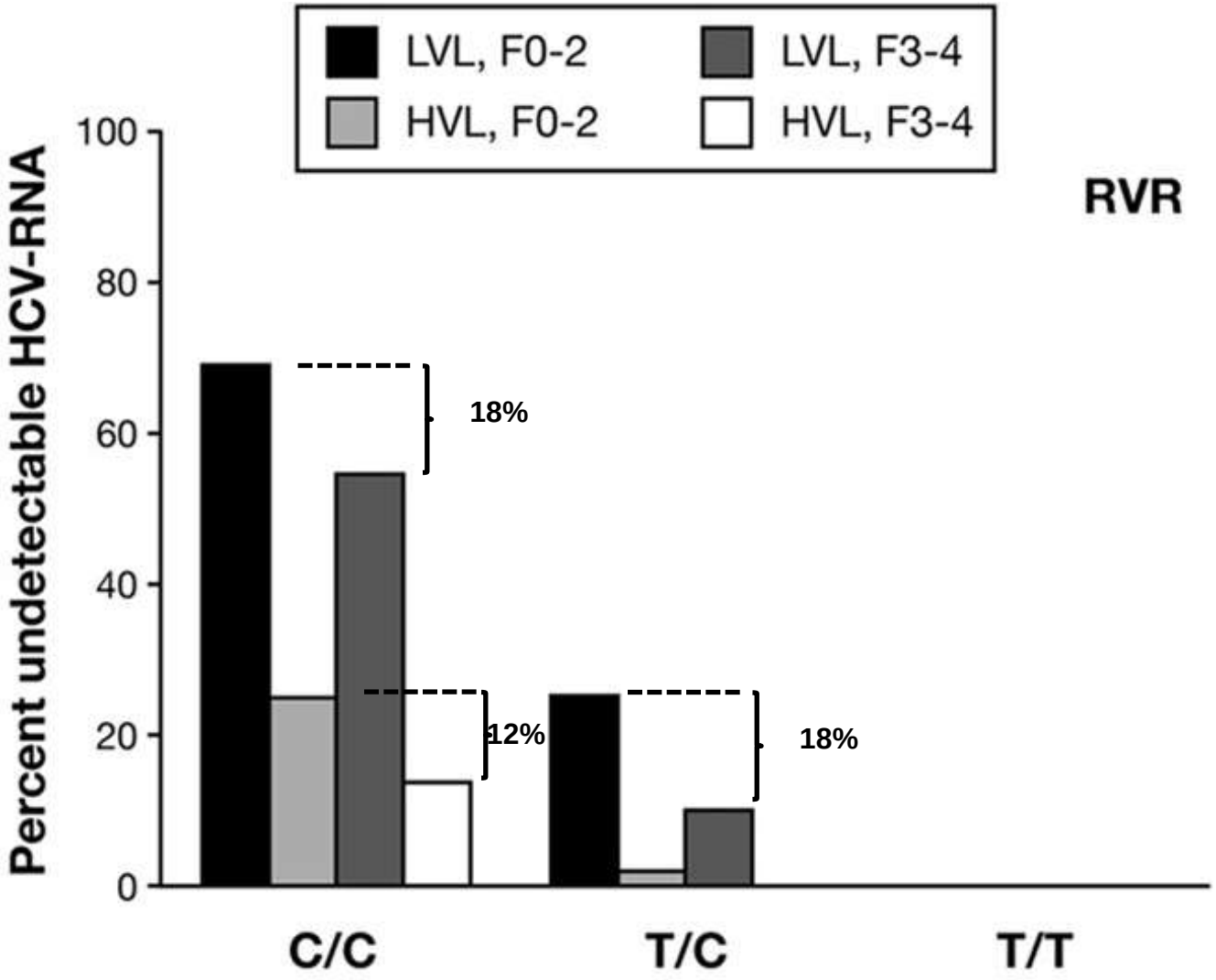


Post hoc analysis of IDEAL trial n=3070

Comparison of RVR vs no RVR + non-CC genotype
Comparison of no-RVR + CC genotype vs no-RVR + non-CC genotype
Co-variates : RVR vs no RVR + CC genotype vs no RVR + non-CC genotype (3-level), ethnicity (4-level), age (≤ 40), gender, BMI (< 30), VL (≤ 600,000), ALT (≤ ULN), fasting glucose (< 5.6), hepatic steatosis (N/Y[>0%]), fibrosis (METAVIR F012), RBV (>13 mg/kg/d)

Thompson AJ, et al Gastroenterology 2010.

RVR is lower in patients with cirrhosis even with IL28B-CC genotype



n=682 Austrian GT1 treatment naïve

Stattemayer, Clin Gastro Hep 2011

Multivariate Analysis of predictive factors for RVR in treatment naïve GT1

Asians

Factor	OR (95%CI)	p value
Female gender	1.91 (1.14–3.19)	0.01
Baseline HCV RNA≤800,000 IU/ml	3.33 (1.96–5.64)	<0.001
Absence of cirrhosis	2.58 (1.39–4.82)	0.003

20-23% had cirrhosis; GT1b=92-4%

Liu, Clin Inf Dis 2008

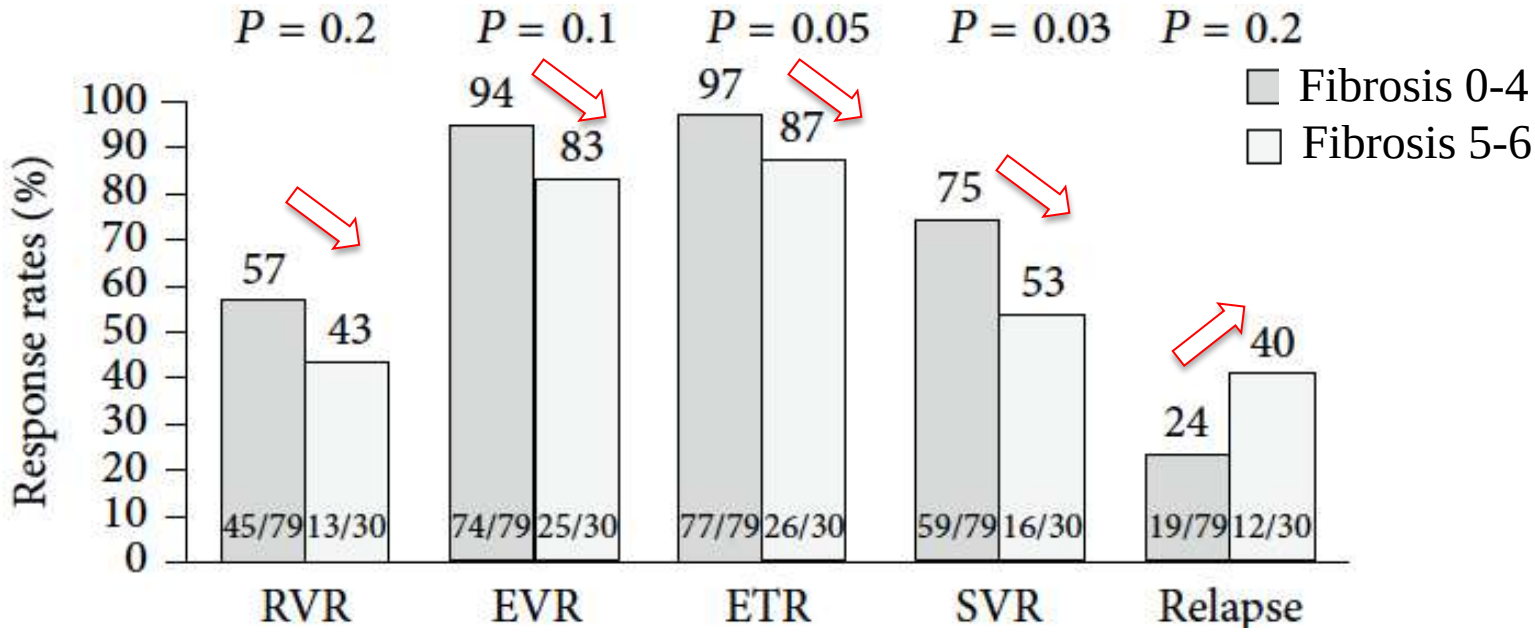
Caucasians

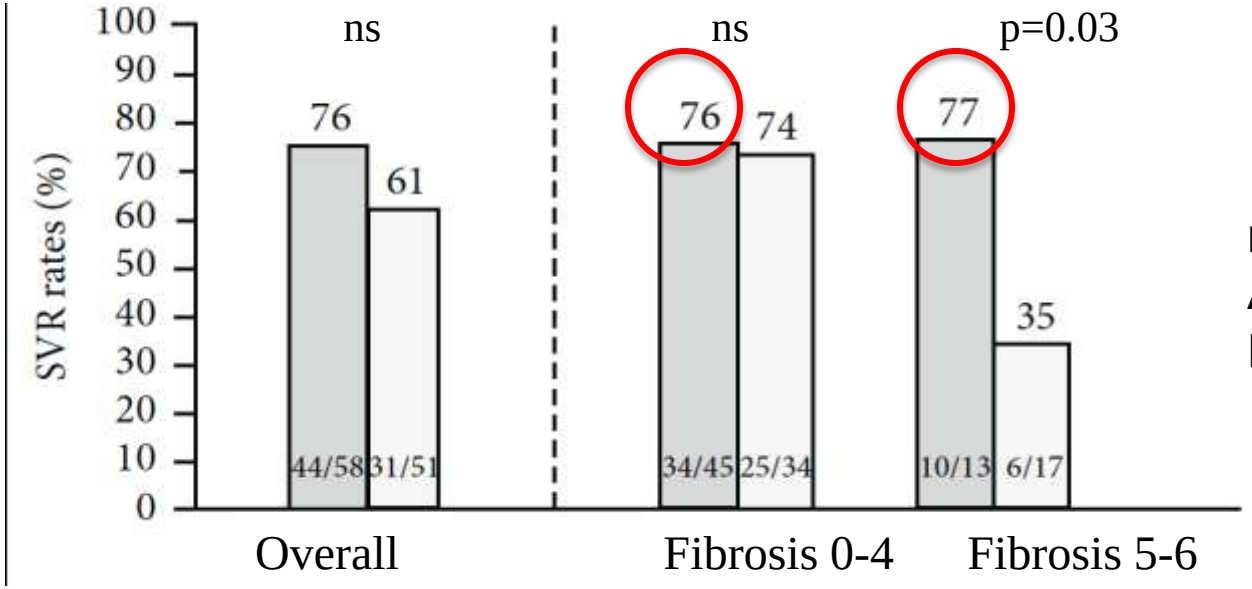
Factor	OR (95%CI)	p value
Baseline HCV RNA≤400,000 IU/ml	2.27 (1.49-3.41)	<0.01
Absence of cirrhosis	1.40 (1.15-1.64)	<0.01

32% had cirrhosis; GT1b=91%

Mangia, Hepatol 2008

SVR in HCV GT1 with IL28B-cc: cirrhosis vs no cirrhosis





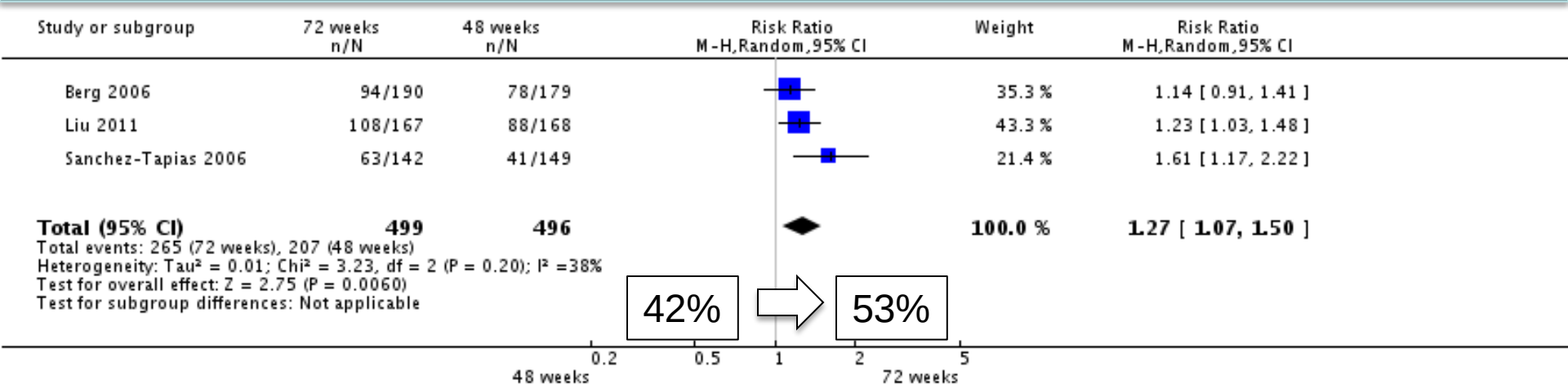
n=109, 27% cirrhosis
All IL28B cc
PR 48w

Aghemo, BioMed Res Int 2013

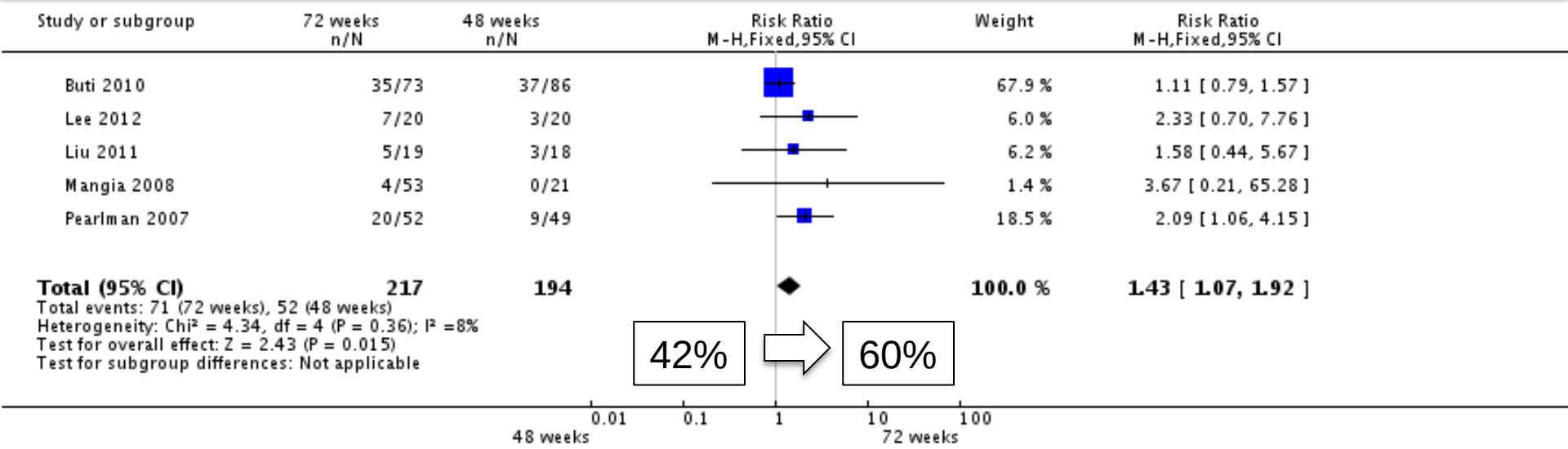
Patients who fail RVR

Systematic Review of extended PR for HCV GT1 Slow Responders

SVR in 48w vs 72w PR in those who fail RVR



SVR in 48w vs 72w PR in those who fail RVR & have ≥2log↓ HCV RNA



Katz, Cochrane Database Systematic Rev 2012

HCV GT1 Treatment Failures

Outcomes in Non-responders to PegIFN/RBV

Study	Treatment	GT	N (Previous Treatment)	SVR Rate (Previous Treatment)
REPEAT[1]	PegIFN alfa-2a + RBV x 48 weeks	1 (> 90%)	473	8%
	PegIFN alfa-2a + RBV x 72 weeks	1 (> 90%)	469	16%
EPIC3[2]	PegIFN alfa-2b + RBV x 48 weeks	1 (81%) 2/3 (15%)	196 (PegIFN alfa-2a) 280 (PegIFN alfa-2b)	6% (PegIFN alfa-2a) 7% (PegIFN alfa-2b)

Outcomes in Relapsers to PegIFN/RBV

Study	Treatment	GT	N (Previous Treatment)	SVR Rate (Previous Treatment)
EPIC3[3]	PegIFN alfa-2b + RBV x 48 weeks	1 (81%) 2/3 (15%)	164 (PegIFN alfa-2a) 180 (PegIFN alfa-2b)	34% (PegIFN alfa-2a) 32% (PegIFN alfa-2b)

1. Jensen DM, et al. AASLD 2007. Abstract LB4.
2. Poynard T, et al. EASL 2008. Abstract 988.
3. Gross J, et al. AASLD 2005. Abstract 60.

DAA therapy in cirrhosis

BOC/P/R combination therapy for HCV G1 compensated cirrhotics: meta-analysis of 5 phase 3 clinical trials

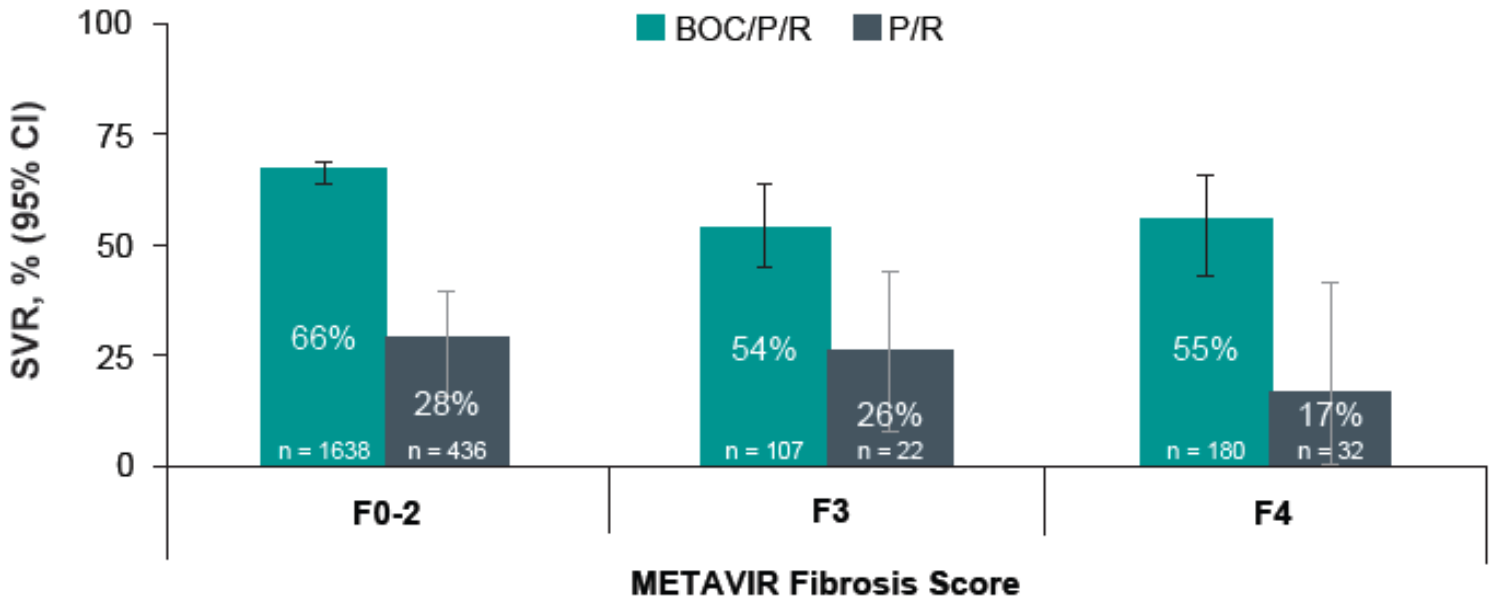
Study	Patients	P/R, n (%)	BOC/P/R 48 weeks, n (%)	BOC P/R RGT, n (%)	All, n (%)	Cirrhotic Patients, n (%)
SPRINT-2	Previously untreated	363 (33)	366 (33)	368 (34)	1097 (100)	53 (5)
Anemia Management study	Previously untreated	—	111 (16)	576 (84)	687 (100)	60 (9)
RESPOND-2	Previous treatment failure	80 (20)	161 (40)	162 (40)	403 (100)	49 (12)
PEG2a	Previous treatment failure	67 (33)	134 (67)	—	201 (100)	33 (16)
PROVIDE	Previous treatment failure	—	134 (100)	—	134 (100)	17 (13)
	Totals	**510 (20)**	**906 (36)**	**1106 (44)**	**2522 (100)**	**212 (8)**

BOC = boceprevir; P/R = peginterferon + ribavirin; RGT = response-guided therapy.

METAVIR stage	Number of patients
F0-2	2074
F3	129
F4	212

Vierlinget al, EASL 2013, #1430

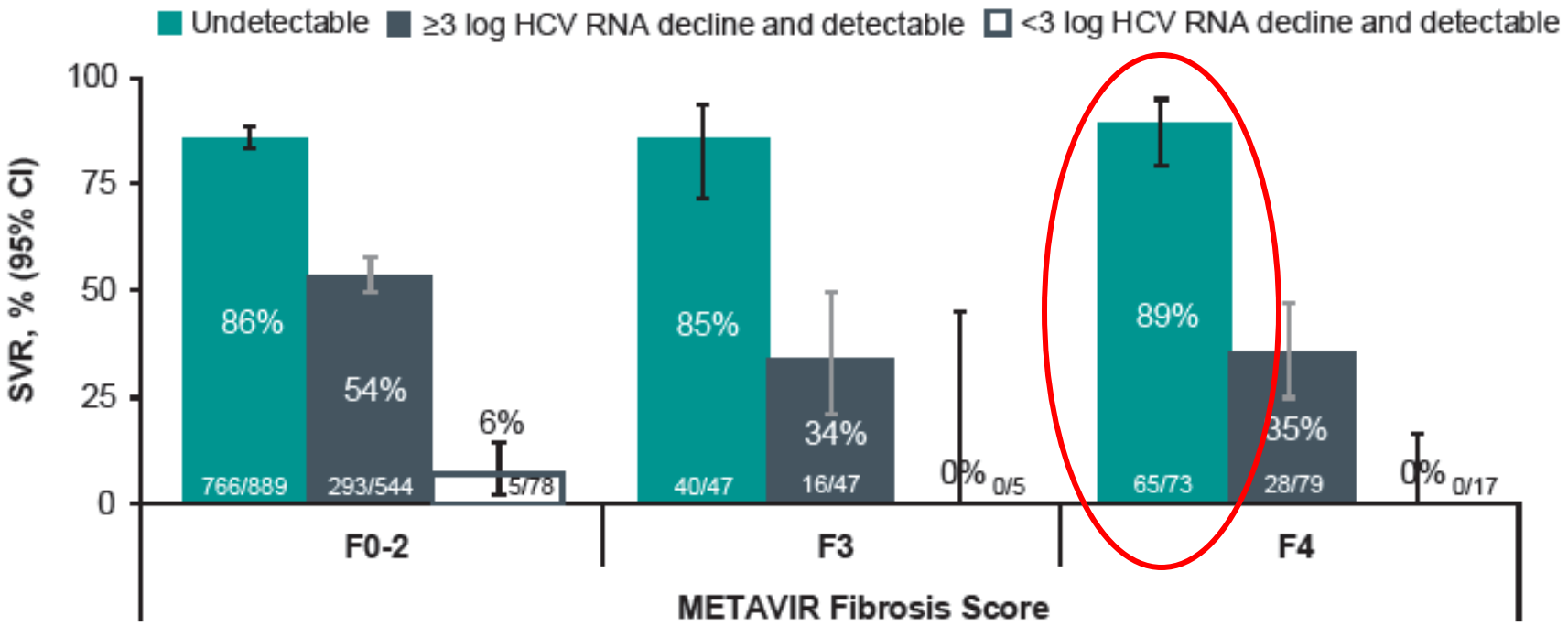
Overall SVR by stage of fibrosis



Overall SVR in PR is low, due to higher numbers of treatment failures in the trials

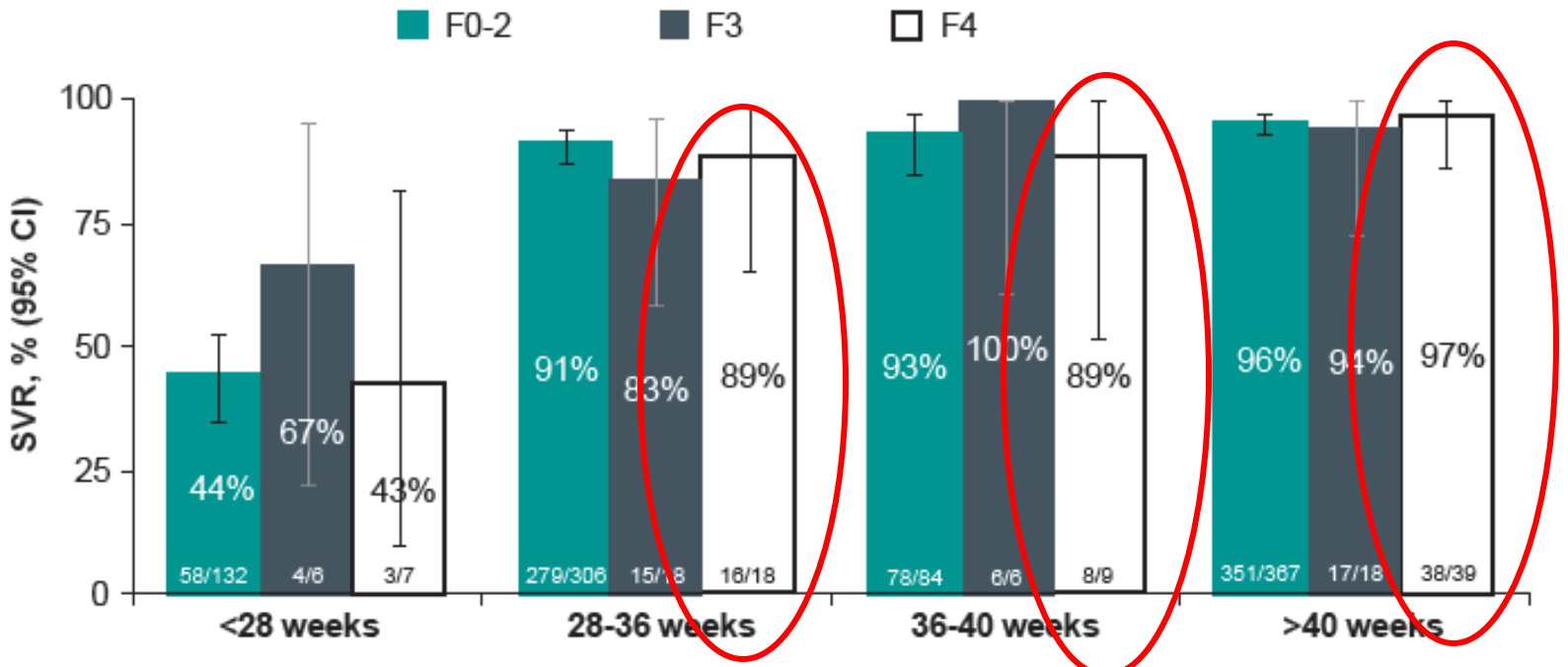
Vierlinget al, EASL 2013, #1430

SVR by week 8 response



Vierlinget al, EASL 2013, #1430

SVR and treatment duration in patients HCV-RNA negative by week 8



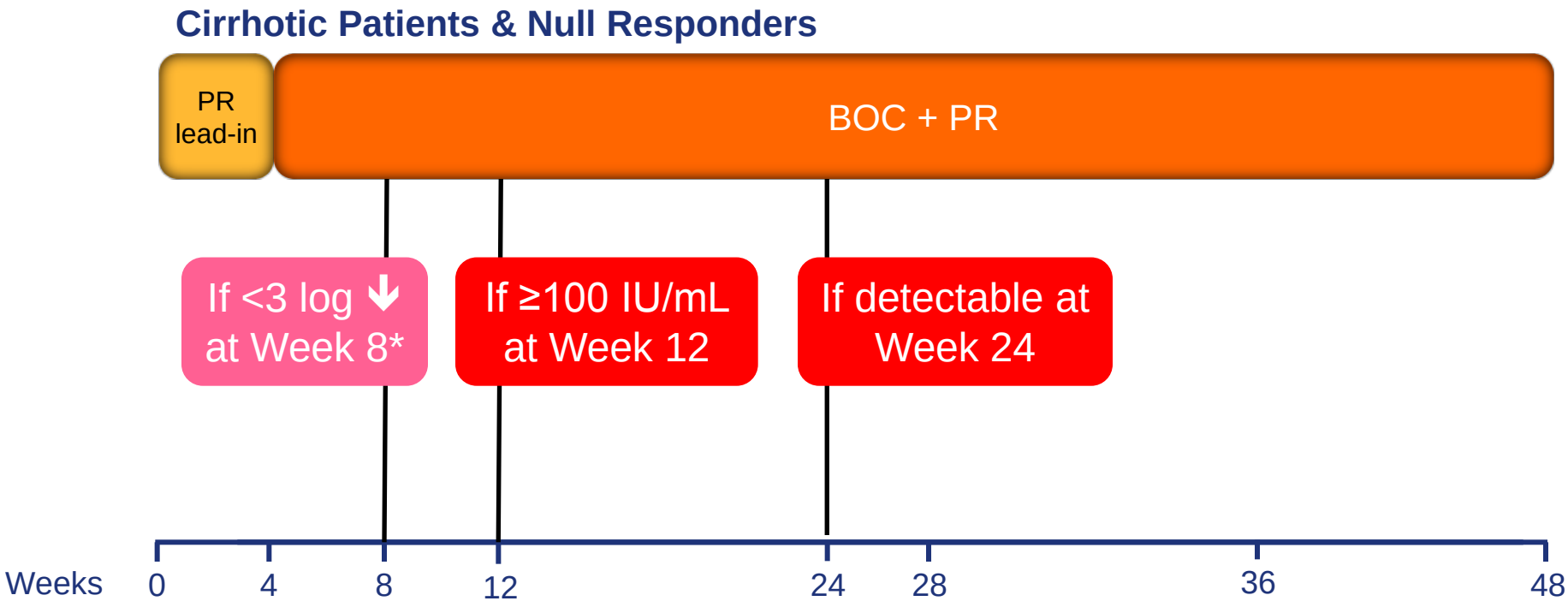
*Treatment-naive patients and those with previous treatment failure combined.

CI = confidence interval; HCV = hepatitis C virus; SVR = sustained virologic response.

Vierling et al, EASL 2013, #1430

Boceprevir regimen summary

- Cirrhotics: 4w lead-in + 44w BPR
- Stop if HCV RNA≥100IU/ml 12w or detectable 24w



VICTRELIS (boceprevir US FDA

Triple Therapy in Real Life Scenarios
- HCV GT 1 cirrhosis
- BNPP Asian Data (BEACprON) will be presented by Prof Pirtvisuth

Decompensated cirrhosis

HCV Decompensated Cirrhosis Trials

Study	Design	Exclusions	No	Discontinue	SVR
Crippin 2002	RCT	Cytopaenias Renal impairment	15	100%	0%
Thomas 2003	Prospective observational	Cytopaenias	20	0	60%
Forns 2003	Prospective observational	Cytopaenias Renal impairment Encephalopathy	30	20%	30%
Everson	Prospective observational	Ascites Renal impairment Non-responders	124	13%	GT1 – 13% GT2/3 – 46%
Iacobellis 2007	Prospective controlled	Rapid deterioration	66	20%	GT1/4 – 7% GT3/4 44%
Iacobellis 2009	Prospective observational	Rapid deterioration Renal impairment	94	19%	GT1/4 – 16% GT3/4 57%
Overall			37/284		GT1 -13%

Study Design

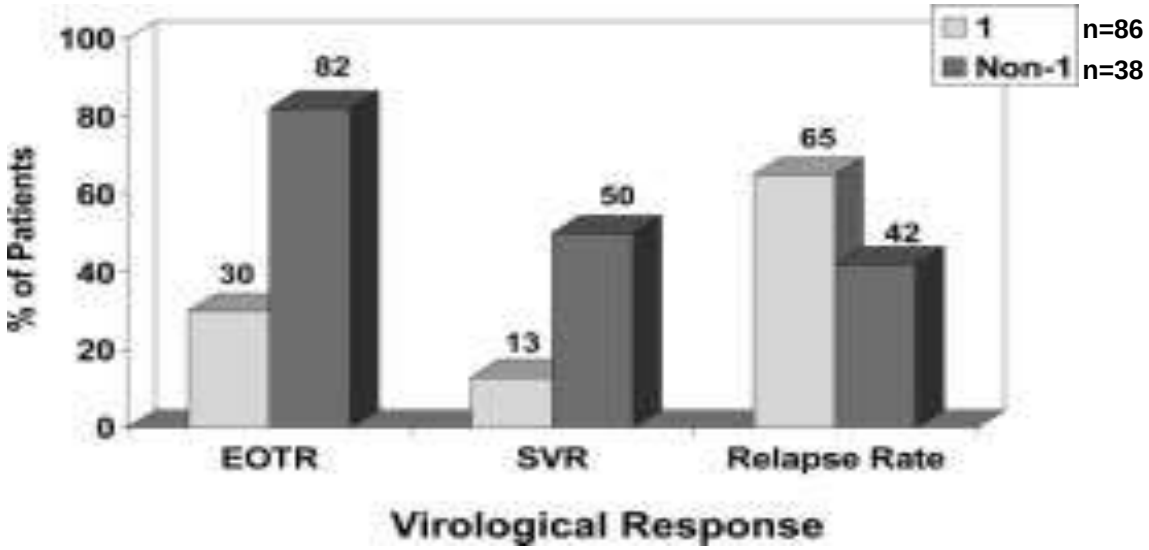
Entry Criteria

- LBx proven cirrhosis
- LBx proven severe fibrosis and
  - Plt <100,000
  - Bil>3mg/dL
  - INR>1.2
  - Alb<3g/dL
  - Collateral/splenomegaly on US
- PHx of clinical complications
  - Ascites
  - Varices
  - SBP
  - encephalopathy

Protocol

- Start low dose
  - Standard IFN 1.5MIU 3x/w
  - pegIFN2b 0.5mcg/kg/w
- Incremental increase 2wkly to max tolerated dose till target dose reached
- Definitions of therapy
  - Full course (achieved target dose and duration)
  - Full duration (reached target duration but not dose)
  - Imcomplete (neither)

Factors Associated with SVR



- Significantly lower rates of end-of-treatment response ($P < .0001$) and SVR ($P < .0001$) in patients with genotype 1 HCV or incomplete course of therapy

Predictor	End-of-Treatment Response, %	SVR, %
Therapy dose & duration		
▪ Full course (n = 36)	83	47
▪ Full duration (n = 22)	82	41
▪ Incomplete therapy (n = 66)	14	6
Virologic response at Week 24		
▪ HCV RNA negative	84	41
▪ HCV RNA positive	4	0

Everson GT, et al. Hepatology. 2005;42:255-262.

Adverse Events during LADR

Adverse events occurred in only 6% of patients (15/124)

Encephalopathy
Sepsis
Worsening ascites
GI bleeding
Pulmonary embolism
Pneumonia
Venous thrombosis
Death (4)

Everson GT. Hepatology 2005; 42: 456

Successful Treatment of severe cholestatic hepatitis with IFN-free regimen

- 54yo African American
- Developed severe cholestatic hepatitis 6m post OLT
- Genotype 1b
- LFT: ALT584, AST 344, bil 1.9mg/dl, INR 1.3
- HCV RNA 12 x10^6 IU/ml
- LBx= fibrosing cholestatic hepatitis
- Immunosuppression: Tac 1.5mg/d, pred 3mg/d

- **Treatment with daclastivir 60mg qd and sofusbuvir 400mg qd for 24w** were used under FDA emergency IND
- Within 4w HCV RNA became negative, pt achieved SVR 24
- No safety issues
- Tac levels did not change during therapy not dose adjustment

Fontana, AASLD 2012 abstract 694

Conclusions

- HCV cirrhosis reduces SVR rates and in decompensated cirrhosis response to therapy is only 13%
- RVR is the most important predictor of SVR in cirrhosis
  - Those who achieve RVR have 90% chance of SVR with 48w PR even in cirrhosis
  - Those who fail RVR only have 35% chance of SVR, and treatment extension to 72w will be needed
- Boceprevir triple therapy in cirrhosis has higher SVR rates that PR in a meta-analysis of phase 3 studies
- In real life situations, advanced cirrhosis and null response has SVR 40% but many adverse events
- Decompensated cirrhosis can be treated carefully with LADR but close monitoring is necessary and SVR is only 13%