Triple therapy with telaprevir or boceprevir: management of side effects

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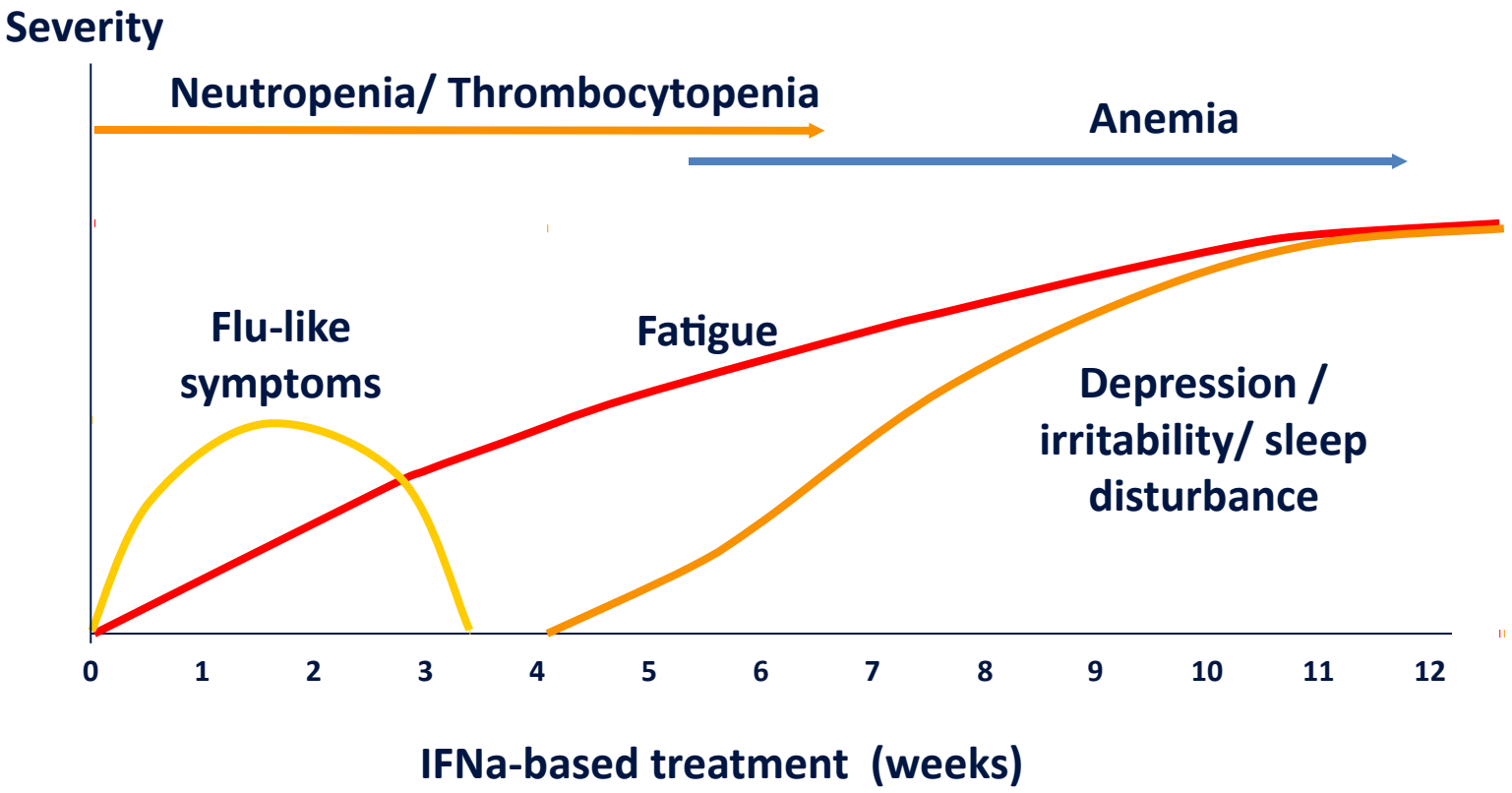
Focus

- Psychiatric side effects
- Hematologic side effects
  - Anemia
    - Frequency
    - Mechanisms
    - Rsik factors and prediction
    - Management
  - Thrombocytopenia

Interferon/ribavirin-related side effects



Aggravation of peginterferon/ribavirin-associated side effects by 1. generation protease inhibitors (PI)?

Side effects	Aggravation due to PI
Depression	-
Fatique	+
Anemia	++
Neutropenia	+
Thrombocytopenia	(+)

German non-interventional study: Telaprevir Triple interim safety analysis at Week 12

Incidence of adverse events (%)	Total population (n=400)
Adverse event (%)	**87**
Mild	**62**
Moderate	**35**
Serious adverse event (%)	**12**
Adverse events occurring in ≥20% of patients (%)	
Psychiatric AEs	**57**
Fatigue	**46**
Gastrointestinal disorders	**38**
Dry skin / pruritus	**37**
Rash	**32**
Anemia	**31**
Anorectal discomfort	**26**
Flu-like symptoms	**26**
Respiratory disorders	**22**

In patients with anemia, RBV dose reduction was reported in 42% of cases and 8% of patients required transfusion

Berg T, et al. EASL 2013: Abstract 793

Management of IFNa-induced depressive disorders und neurpsychiatric side effects?

Strategies

Preemptive/prophylactic treatment

Wait and treat if symptoms occur

ORIGINAL RESEARCH | Annals of Internal Medicine

Escitalopram for the Prevention of Peginterferon-α2a–Associated Depression in Hepatitis C Virus–Infected Patients Without Previous Psychiatric Disease

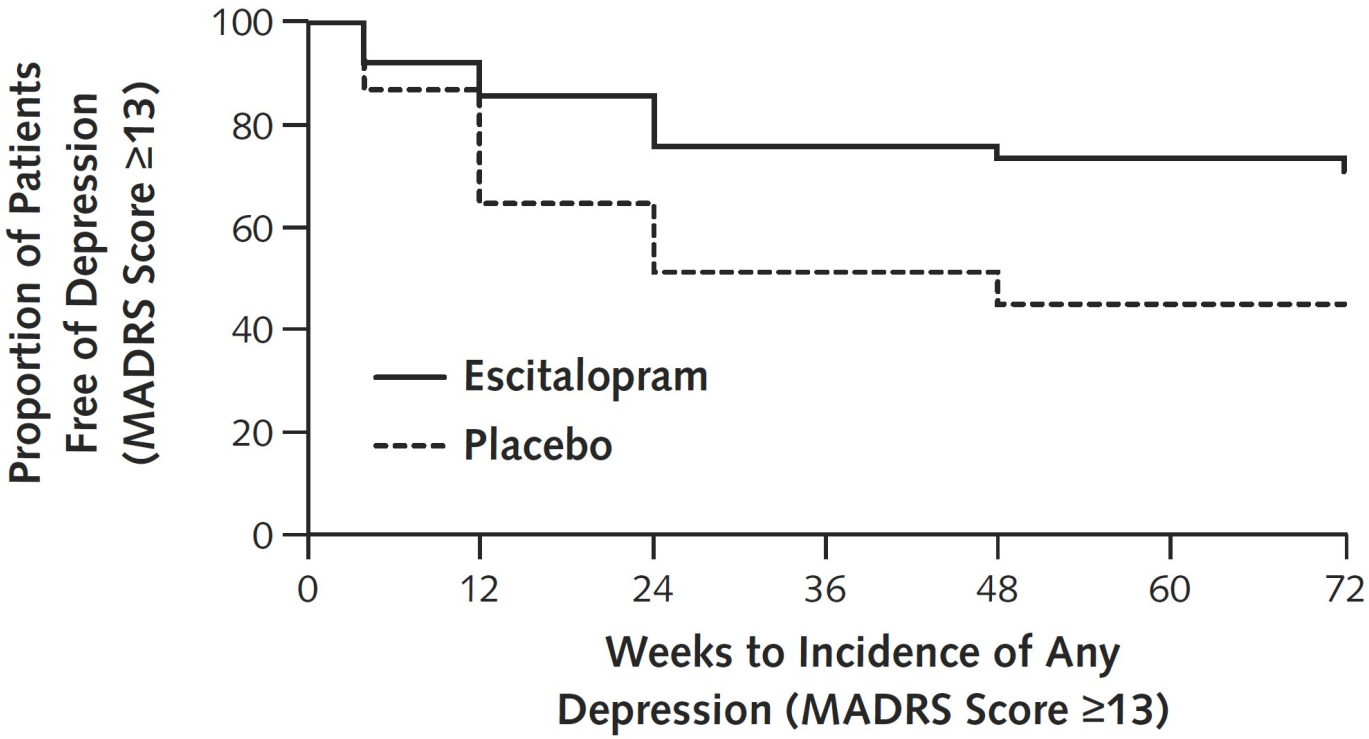
A Randomized Trial

Martin Schaefer, MD; Rahul Sarkar, MD; Viola Knop, MD; Susanne Effenberger, MSc; Astrid Friebe, MD; Loni Heinze, MD; Ulrich Spengler, MD; Thomas Schlaepfer, MD; Jens Reimer, MD; Peter Buggisch, MD; Johann Ockenga, MD; Ralph Link, MD; Michael Rentrop, MD; Hans Weidenbach, MD; Gwendolyn Fromm, MD; Klaus Lieb, MD; Thomas F. Baumert, MD; Andreas Heinz, MD; Thomas Dischер, MD; Konrad Neumann, PhD; Stefan Zeuzem, MD; and Thomas Berg, MD

Ann Intern Med. 2012;157:94-103.

Prevention of Interferon-induced depression

Schaefer M et al. Ann Intern Med 2012; 157: 94

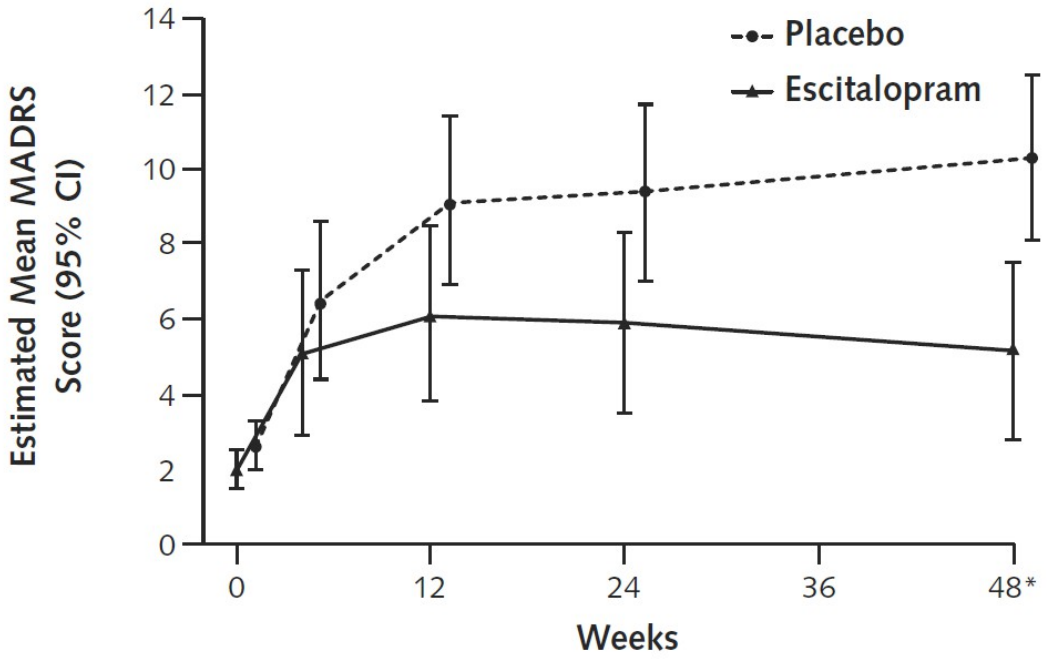


Escitalopram, *n*	90	89	80	71	60	40
Placebo, *n*	91	91	79	56	40	25

Prevention of Interferon-induced depression

Schaefer M et al. Ann Intern Med 2012; 157: 94

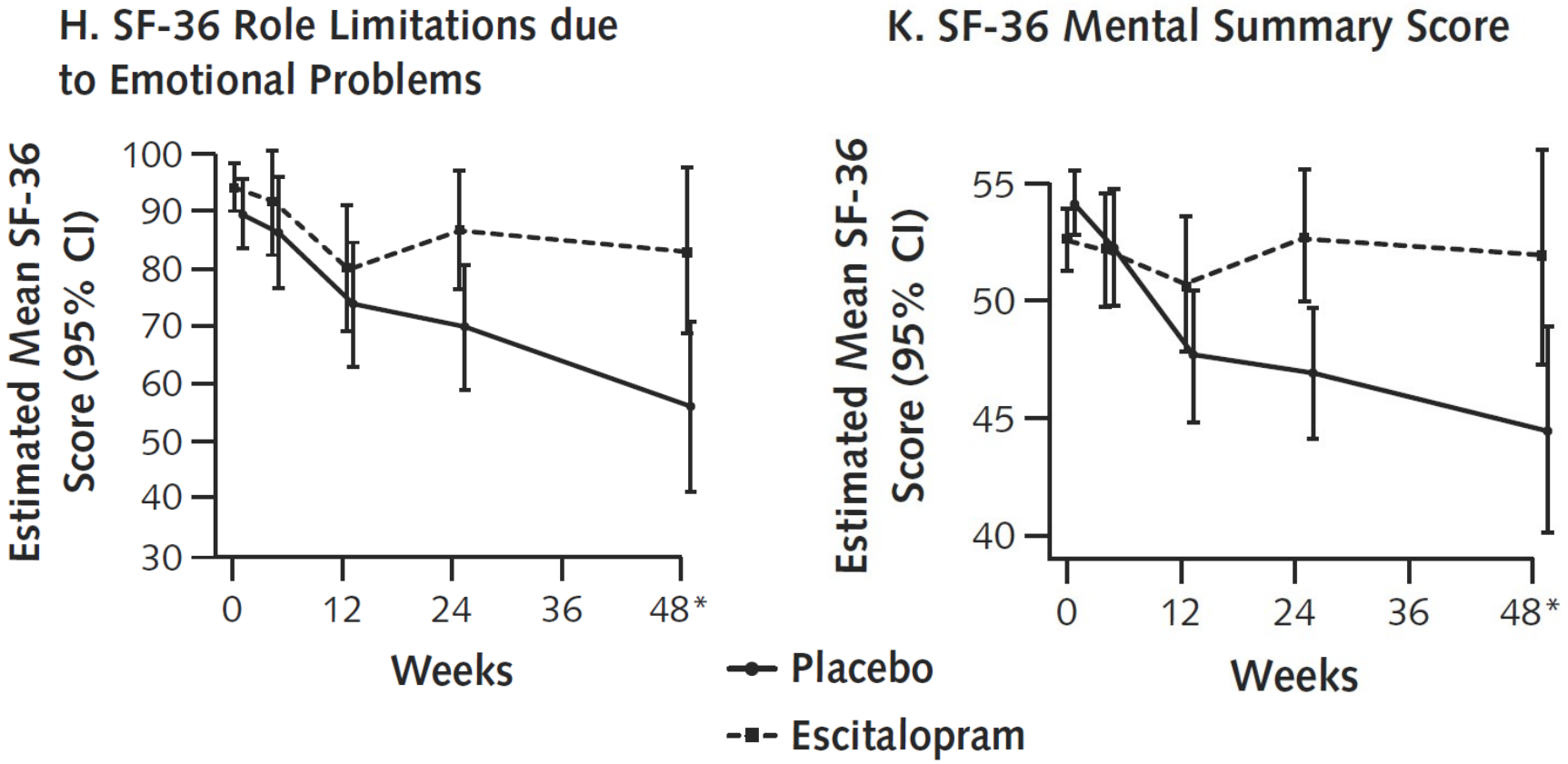
MADRS during treatment



Escitalopram, *n*	90	89	80	77	45
Placebo, *n*	91	91	86	76	48

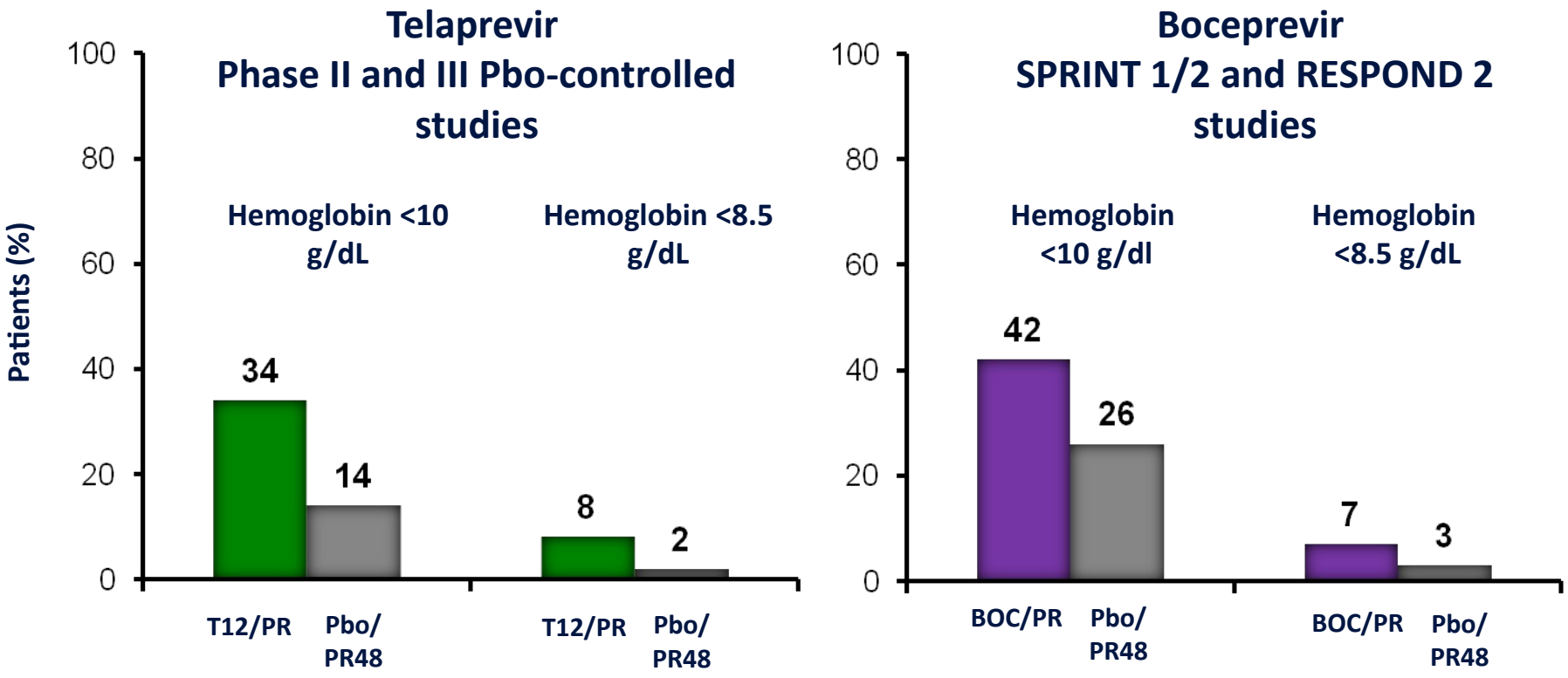
Prevention of Interferon-induced depression

Schaefer M et al. Ann Intern Med 2012; 157: 94



Anemia

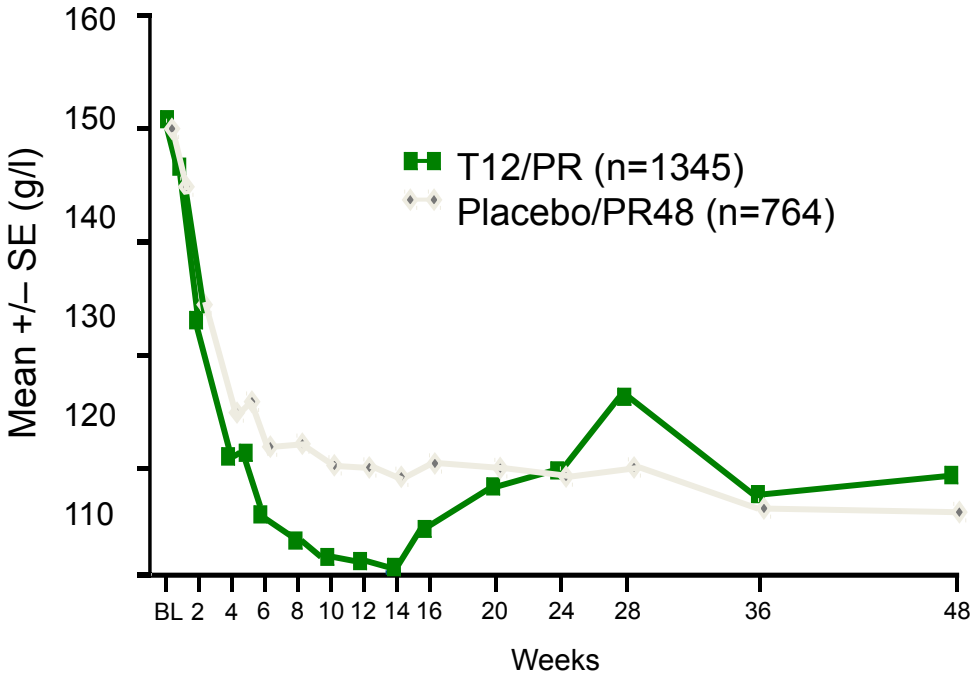
Frequency of anemia with telaprevir and boceprevir



Telaprevir EU SmPC; Boceprevir FDA Advisory Committee briefing document

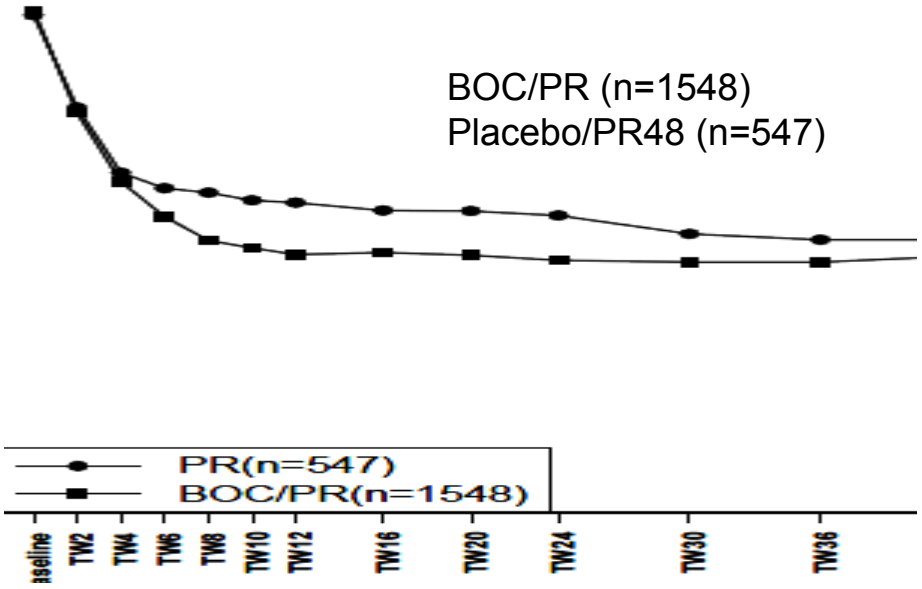
Hemoglobin shifts on telaprevir and boceprevir treatment

Mean Hb values over time in TVR phase 2 and 3 Pbo-controlled studies



- Anemia was managed by RBV dose reduction
- 21.6% of TVR treated patients vs 9.4 with PR
- 1% of patients received EPO

Mean Hb values over time in BOC SPRINT 1/2 and RESPOND 2 studies

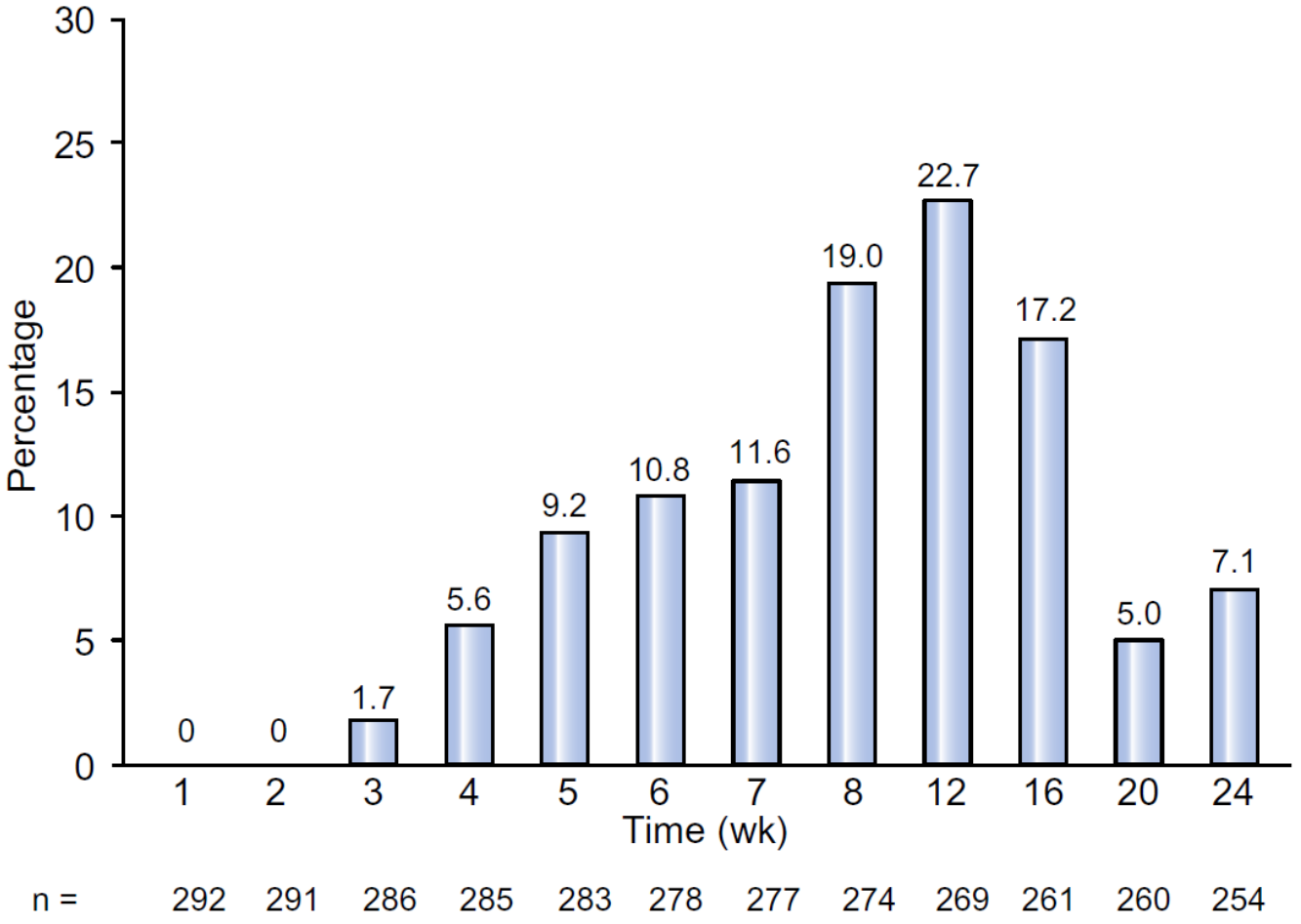


- Anemia was managed by EPO and RBV dose reduction
- 26% of BOC treated patients had RBV DR vs 13% with PR
- 43% of BOC-treated patients received EPO vs 26% with PR

Telaprevir and Boceprevir FDA Advisory Comittee briefing documents
Telaprevir and Boceprevir EU SmPCs

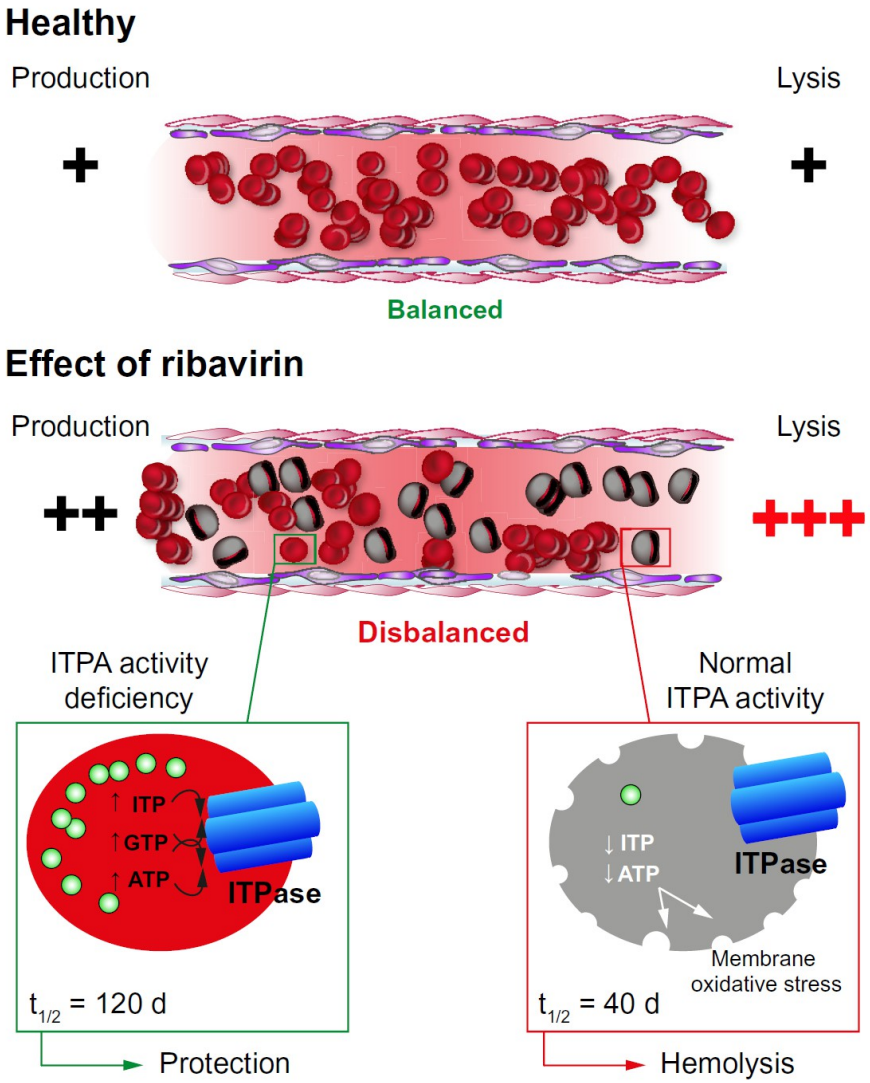
Percentage of patients experiencing on-treatment severe anemia (hemoglobin < 8.5 g/dL) during telaprevir triple

Ogawa E et al. J Hepatol 2013; 59: 667



Mechanisms of anemia development

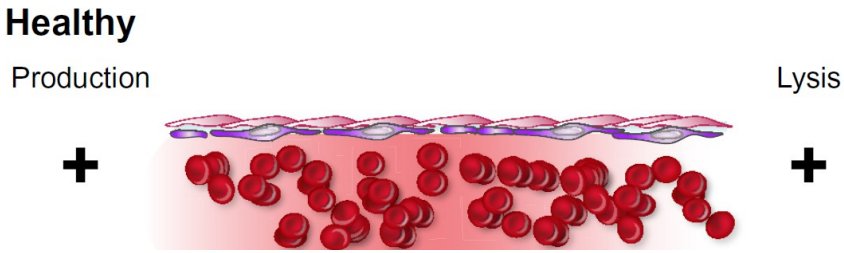
Mechanisms of ribavirin-induced anemia



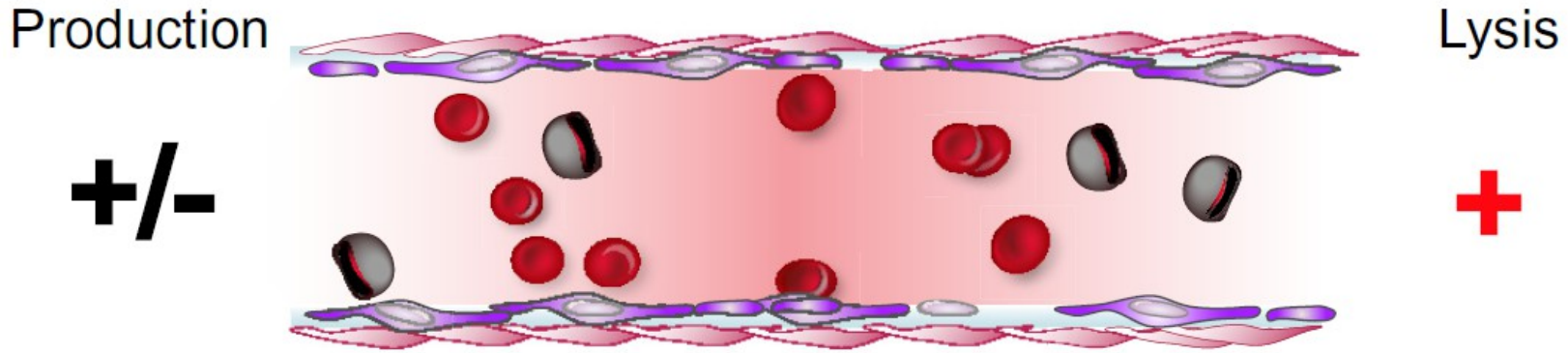
ITPA = Inosine Triphosphate Pyrophosphatese

Romero-Gomez M et al. J Hepatol 2013; 59: 1323

Mechanisms of ribavirin-induced anemia



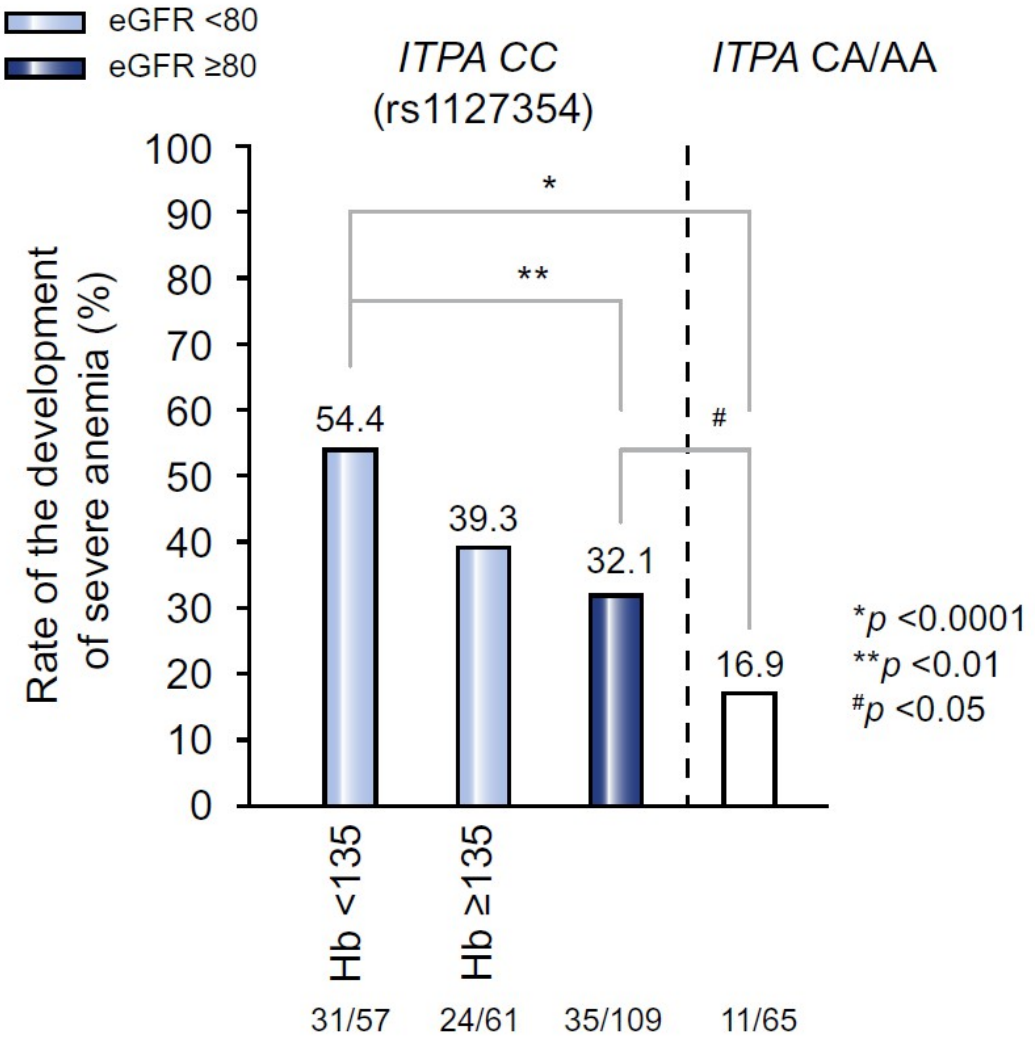
Effect of protease inhibitors



Romero-Gomez M et al. J Hepatol 2013; 59: 1323

Percentage of patients developing severe anemia (hemoglobin < 8.5 g/dL) stratified by ITPA SNPs, baseline GFR, and Hb levels

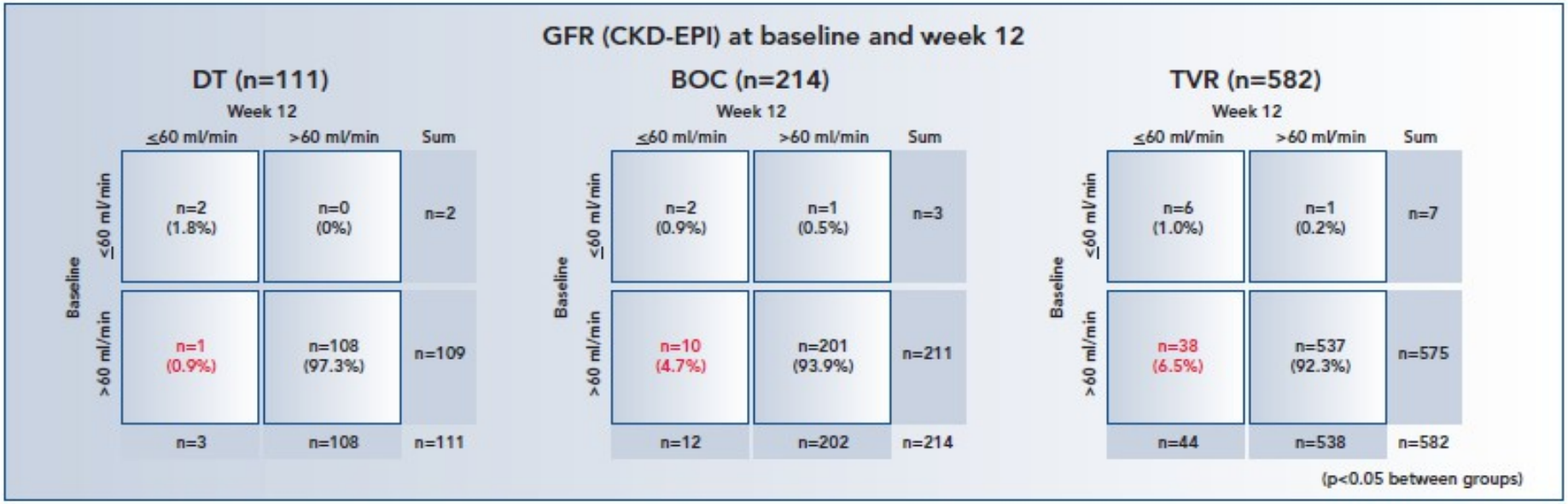
Ogawa E et al. J Hepatol 2013; 59: 667



ITPA = inosine triphosphatase

Kidney function and first generation protease inhibitors (Telaprevir and Boceprevir)

eGFR change from baseline to week 12



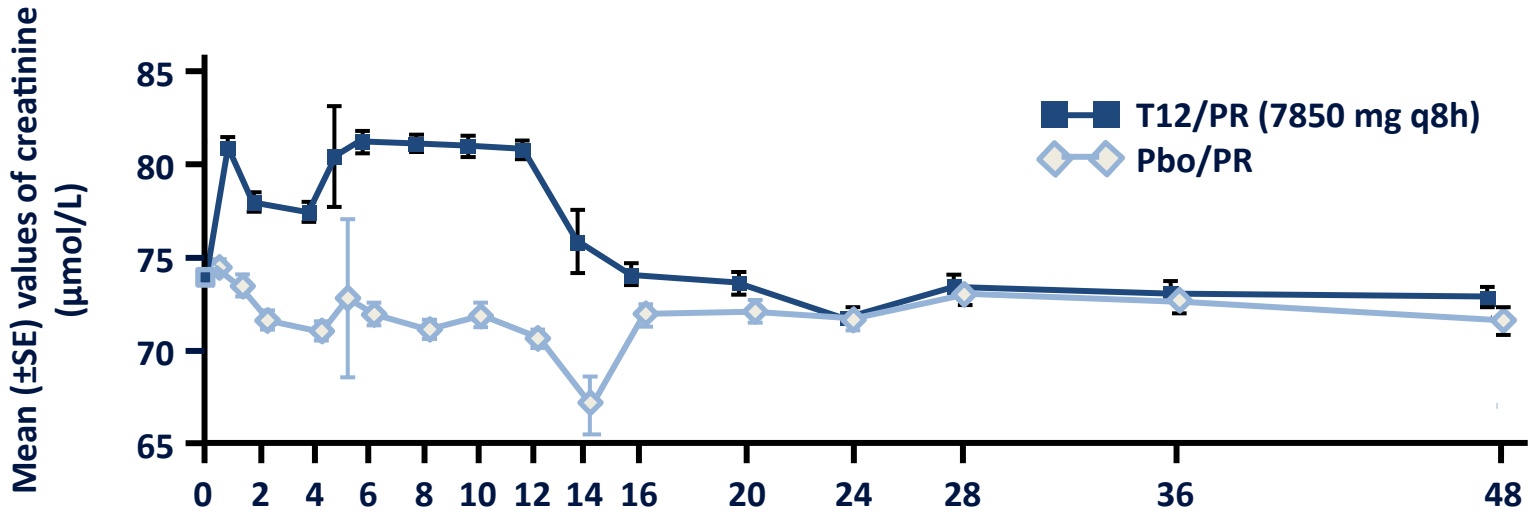
Dual Therapy

Boceprevir (BOC) Triple

Telaprevir (TVR) Triple

Mauss S et al Hepatology 2013

Creatinine levels over time during TVR treatment1

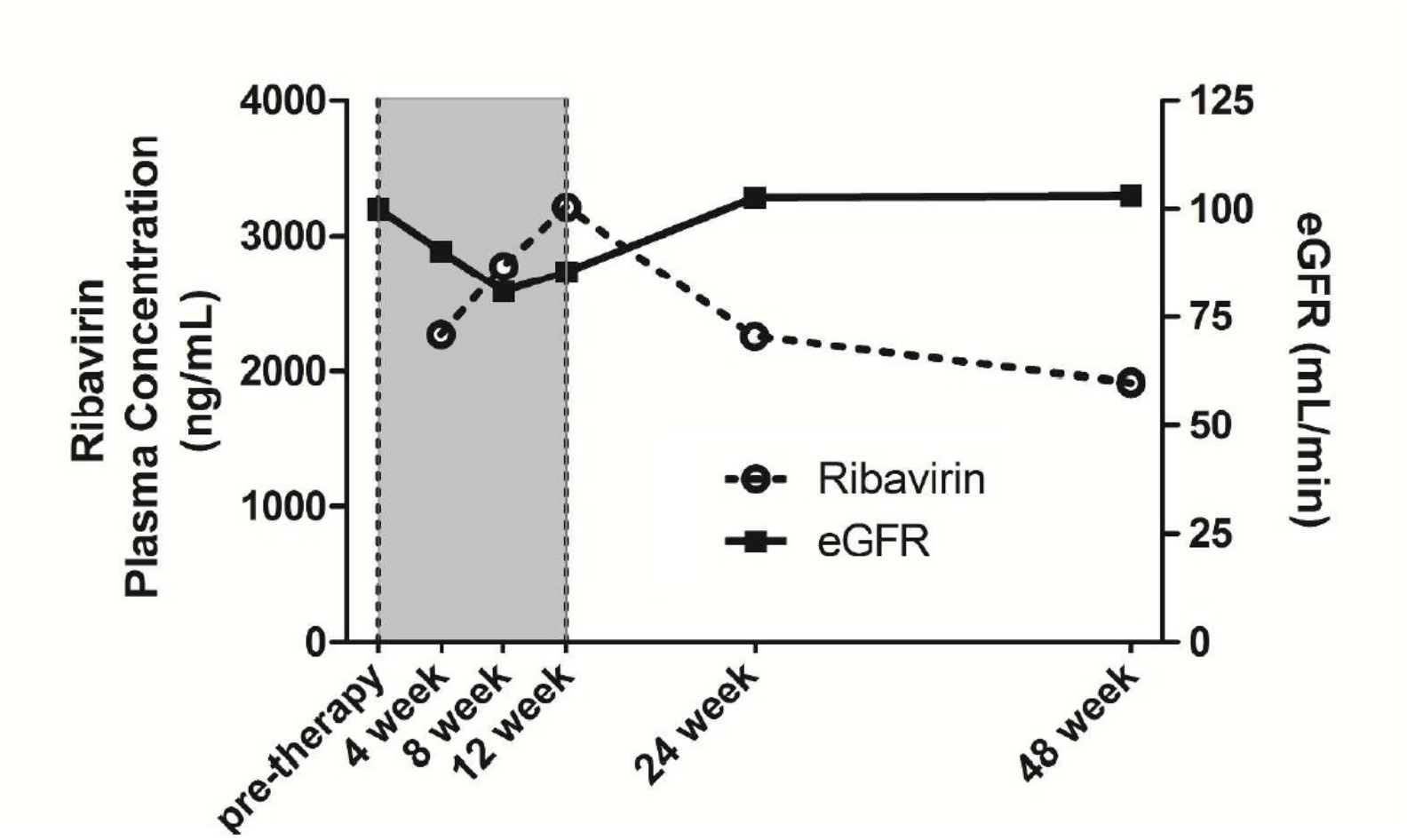


No. of subjects										
T12/PR (750 mg q8h)	1346	1310	1262	1224	614	606	1018	466	551	527
Pbo/PR	764	750	727	686	534	501	564	449	405	382

- Telaprevir use was associated with an on-treatment increase in serum creatinine of 5–10 µmol/L, which was readily reversible on discontinuation. It is unclear whether this is an effect on the glomerular filtration rate or on creatinine disposition. The identification of older age and hypertension as risk factors for this side effect may indicate the former. This effect appears reversible on discontinuation of telaprevir2
- Serum creatinine evaluation is recommended as frequently as the haematology evaluations (at weeks 2, 4, 8 and 12 or as clinically indicated)3

1. Antiviral Drugs Advisory Committee. Telaprevir 375-mg Film-Coated Tablet for the Treatment of Genotype 1 Chronic Hepatitis C Briefing Document. Published April 28, 2011
2. Data on File; 3. Telaprevir EU SmPC

Effect of TVR triple therapy on eGFR and ribavirin plasma concentration



Tempestilli M et al. Hepatology 2013; epub

Prediction of significant anemia development

Predictive factors associated with anemia in patients treated with dual or first generation triple therapy

Type of treatment/Factor	Dual therapy	Triple therapy with telaprevir	Triple therapy with boceprevir
Age	>50 yr	>50 yr	>40 yr
Sex	Female	Female in univariate analysis	Female
Body mass index		<23 kg/m^2	
Statin use			Statin use
Baseline hemoglobin levels	Lower baseline hemoglobin levels	Lower baseline hemoglobin levels	Lower baseline hemoglobin levels
Stage of disease	Cirrhosis	Advanced fibrosis	Advanced fibrosis
Renal function	Creatinine >1.5 mg/dl; creatinine clearance <80 ml/min		Creatinine clearance <80 ml/min
Ribavirin dose	>12 mg/kg		
ITPA polymorphism	*ITPA* polymorphism	*ITPA* polymorphism	*ITPA* polymorphism
On-treatment factors	Fast hemoglobin drop during the first weeks of treatment (>1.5-2 g/dl at week 2)	Low hemoglobin levels (<13 g/dl) at week 2	Degree of hemoglobin decrease during the lead-in phase

Romero-Gomez M et al. J Hepatol 2013; 59: 1323

TVR + PEG-IFNa-2a plus RBV in Tx-Naïve Patients with G1 and Mild to Moderate Liver Disease – Results (N=1642)

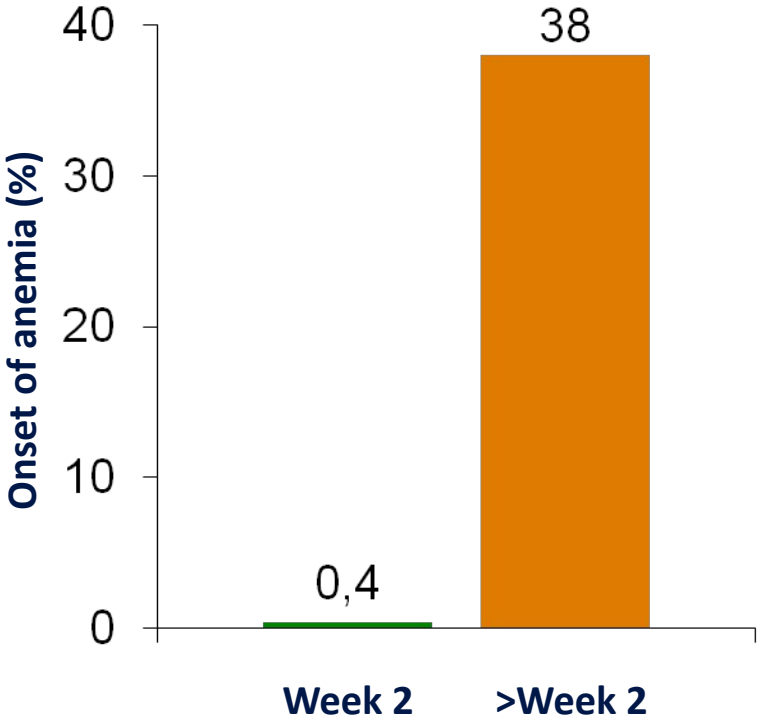
	F0-1 (n=630)	F2 (n=580)	F3 (n=247)	F4 (n=185)
24 weeks PR [%]	66	57	53	55
RVR [%]	73	73	61	57
SVR [%]	80	79	68	54
Grade 2-4 AEs	75	79	85	88
SAEs	9	10	11	17
Discontinuation due to AE	7	12	13	15
Grade 2-4 rash SSC AE*	19	18	26	25
Hb <10 g/dL#	42	43	47	55
Hb ≤8.5 g/dL	12	12	19	21

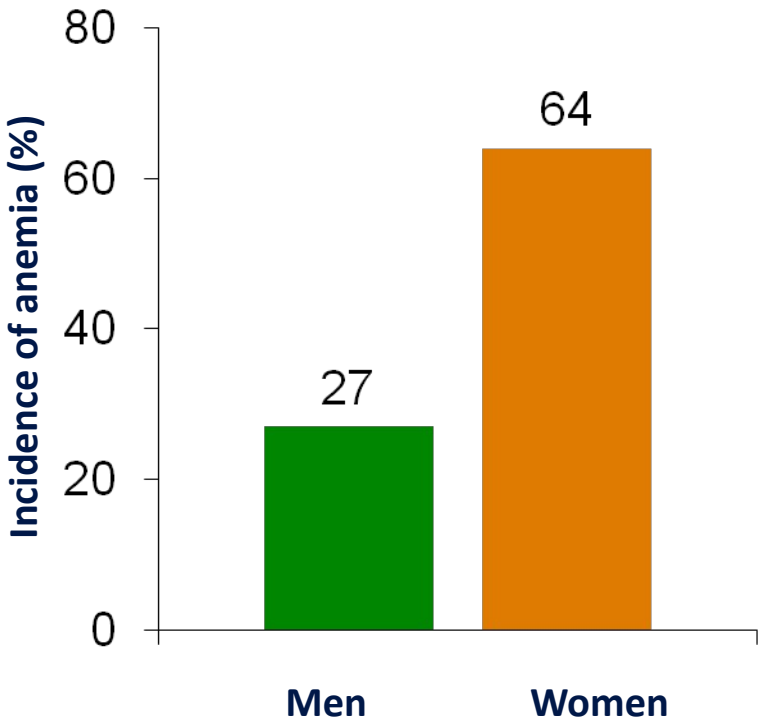
*Any rash SSC clinical AE #includes ≤8.5 g/dL

Zeuzem et al, AASLD 2013, poster (1908)

Occurence of anemia

- Anemia (Hb <10 g/dL) occurred during treatment in 38% of patients*





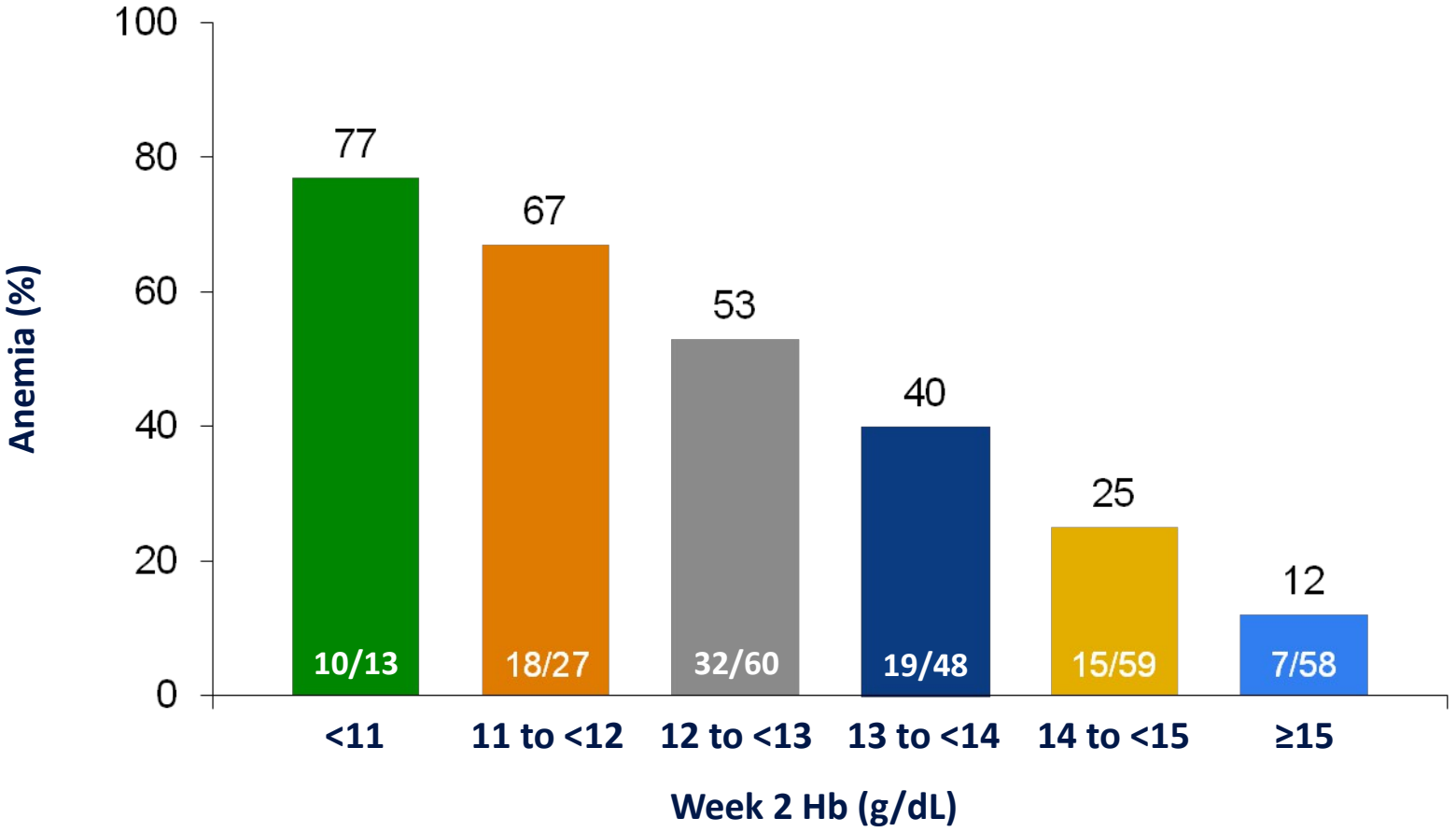
- Anemia was most frequently seen after Week 2
- The greater incidence of anemia observed in women was partly explained by lower baseline Hb levels compared with men

*Hb data available for n=265 in T21/PR48 group

Zeuzem S et al. AASLD 2012

Patients experiencing on-treatment anemia after Week 2: Hb level

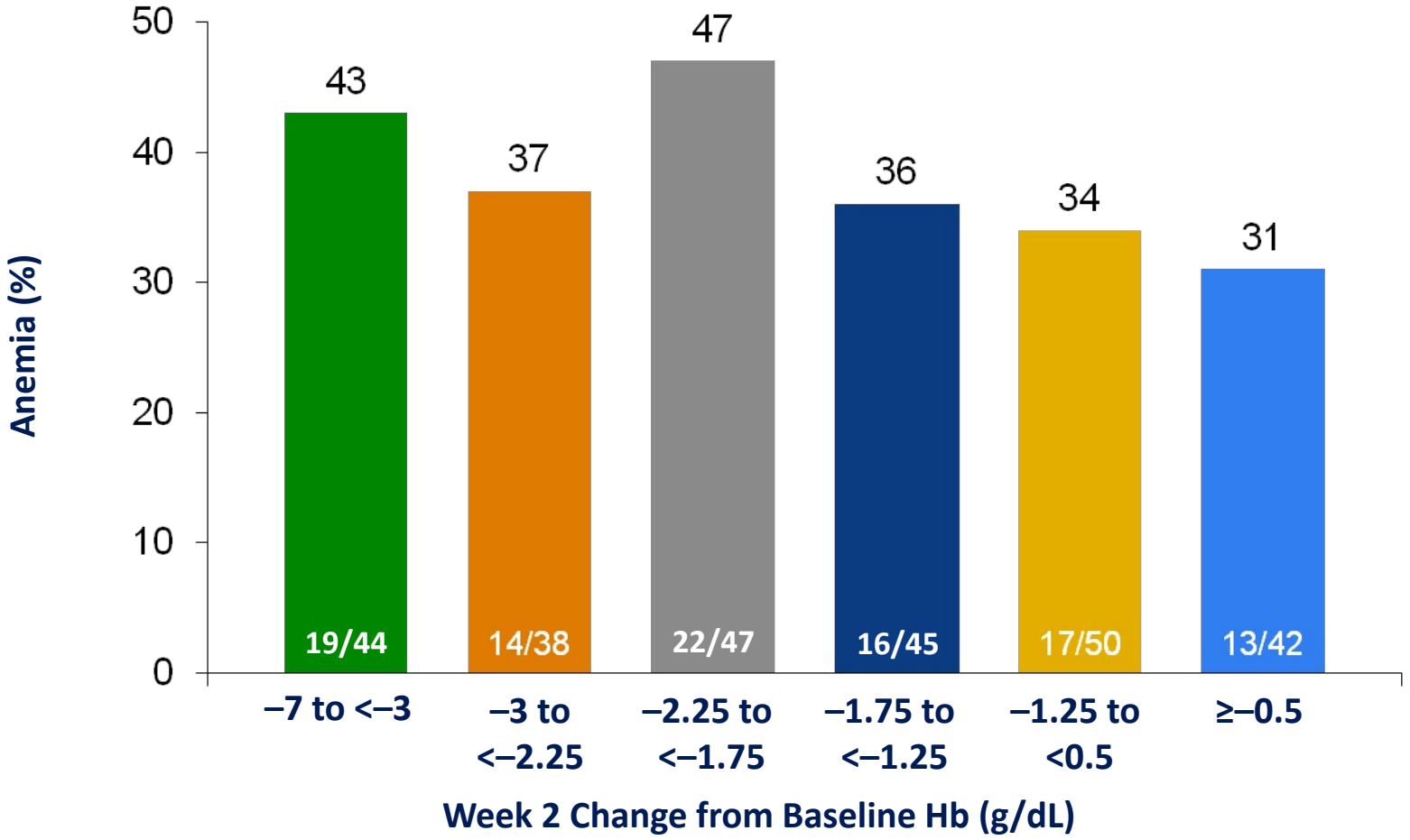
- **Absolute Hb level at Week 2 was correlated with subsequent development of on-treatment anemia**



Zeuzem S et al. AASLD 2012

Patients experiencing on-treatment anemia after Week 2: change in Hb level

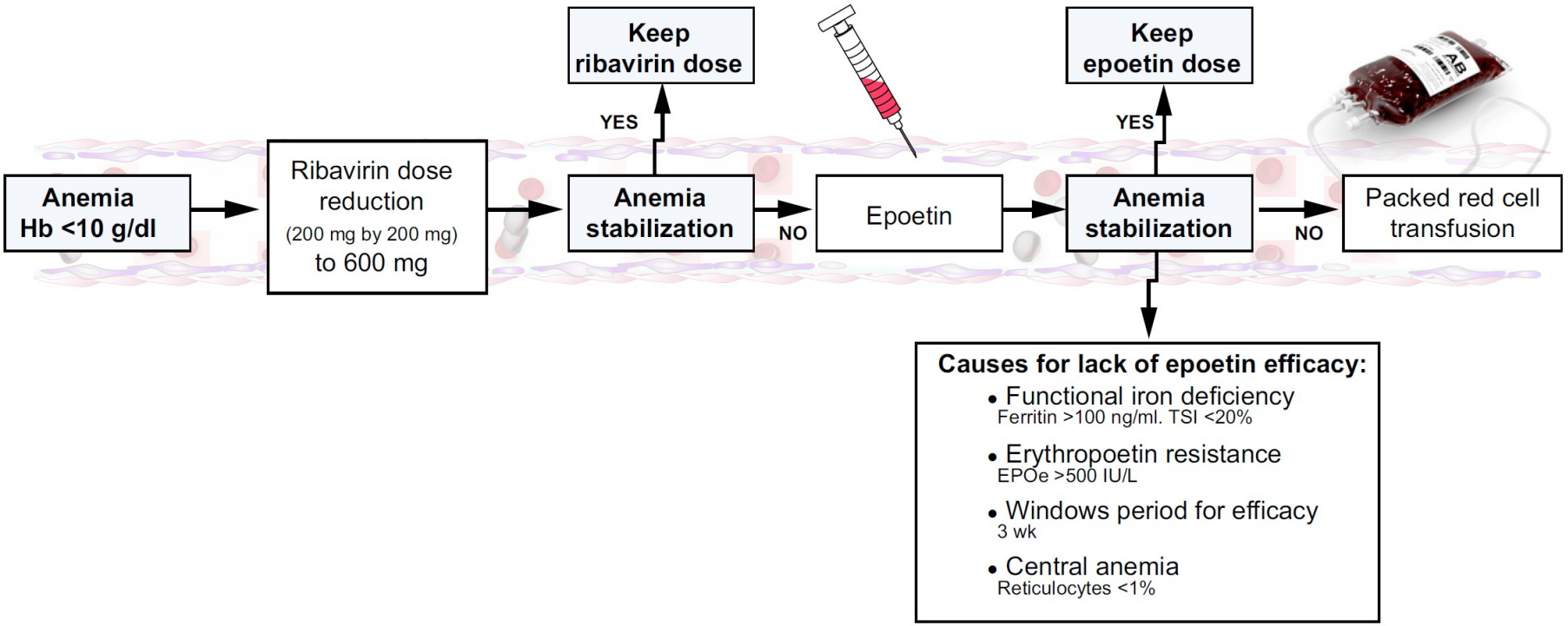
- Change in Hb level from baseline to Week 2 did not predict subsequent development of on-treatment anemia



Zeuzem S et al. AASLD 2012

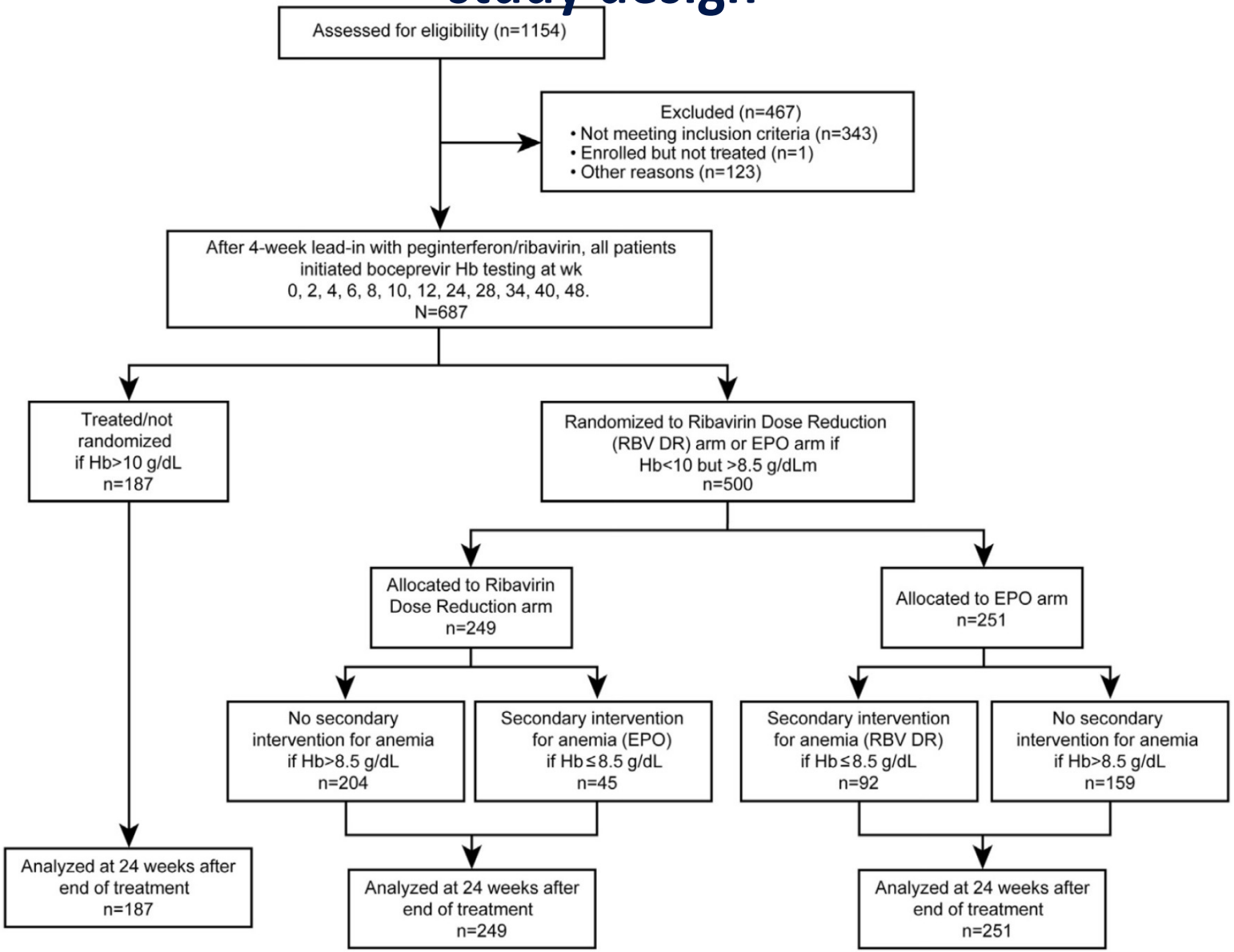
How to manage anemia

Proposed algorithm for the management of first generation protease-inhibitor-based triple therapy



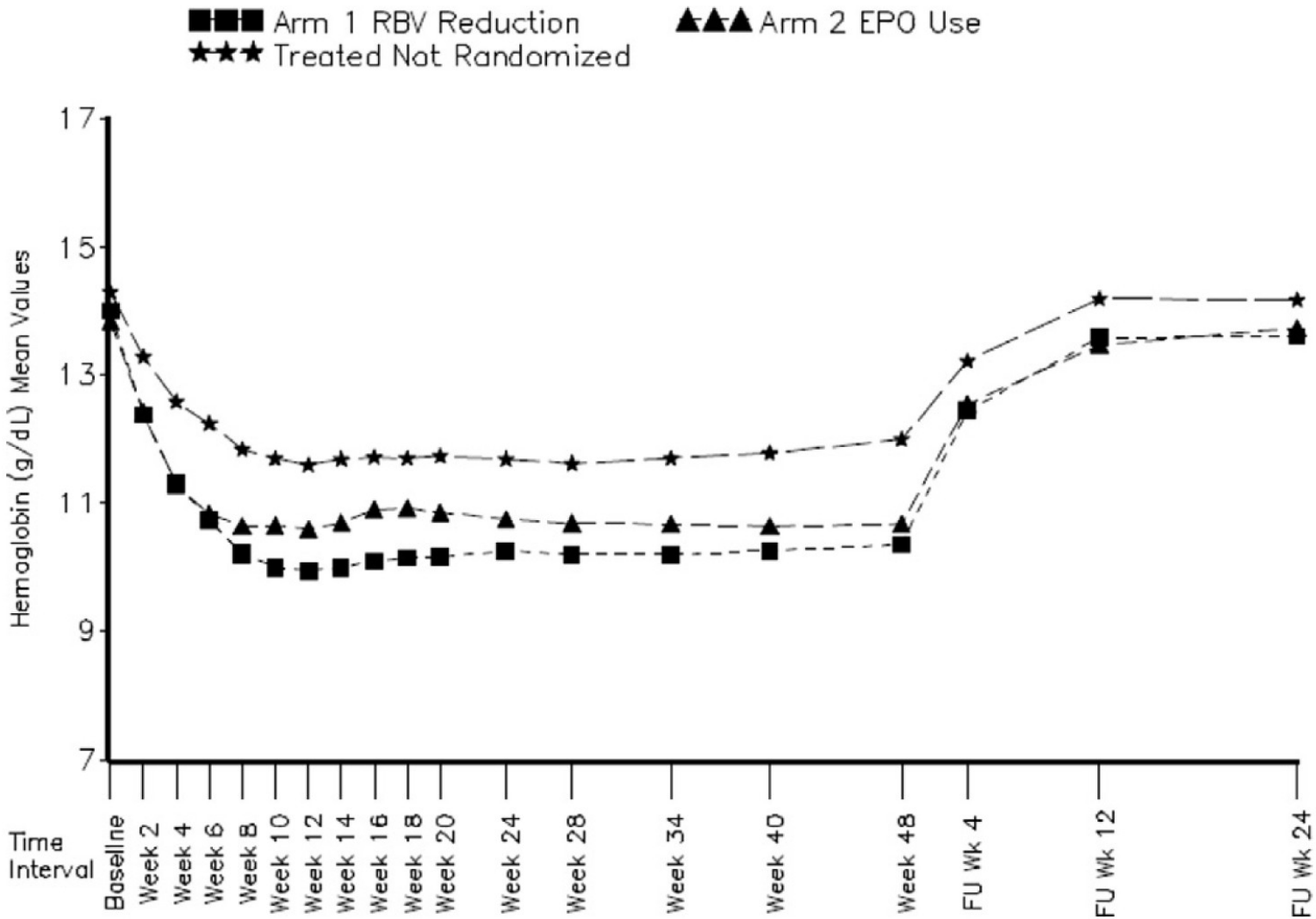
Romero-Gomez M et al. J Hepatol 2013; 59: 1323

BOC Triple induced anemia: Epo or RBV dose reduction: study design



Poordad F et al. Gastroenterology 2013; 145: 1035

Management of anemia: Epo or RBV dose reduction?



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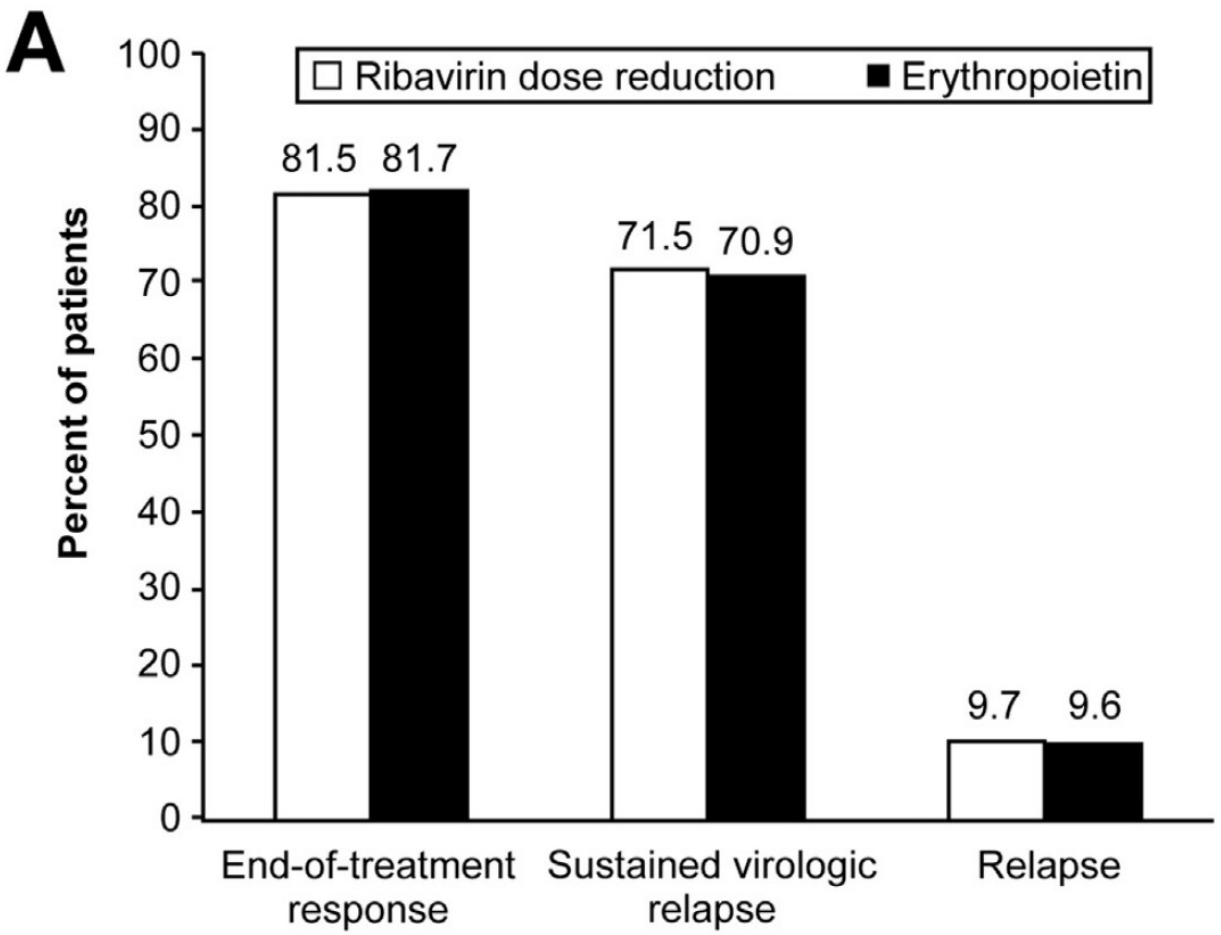
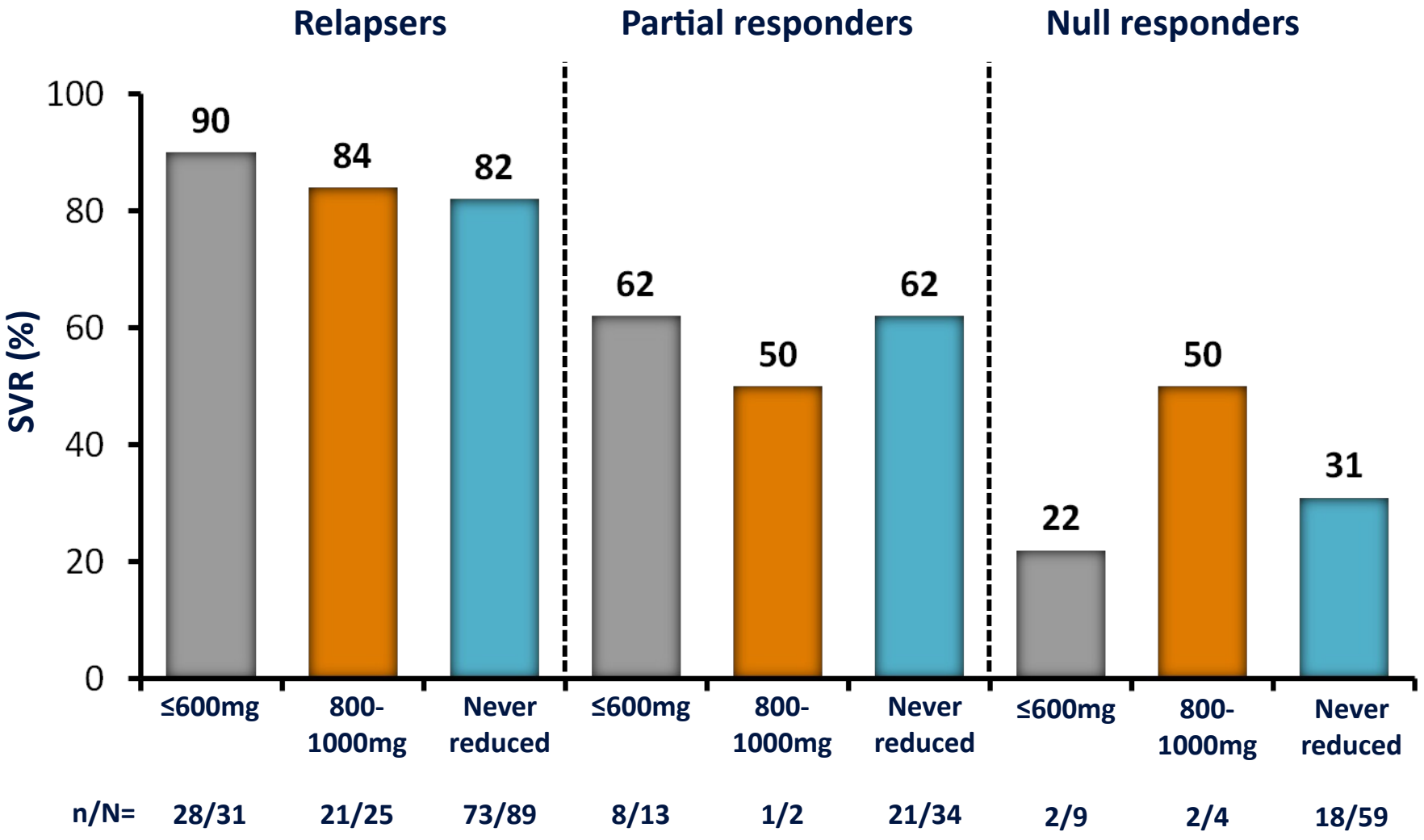
Management of anemia: Epo or RBV dose reduction?



Poordad F et al. Gastroenterology 2013; 145: 1035

No impact of RBV dose reduction on SVR with telaprevir (REALIZE: T12PR48)

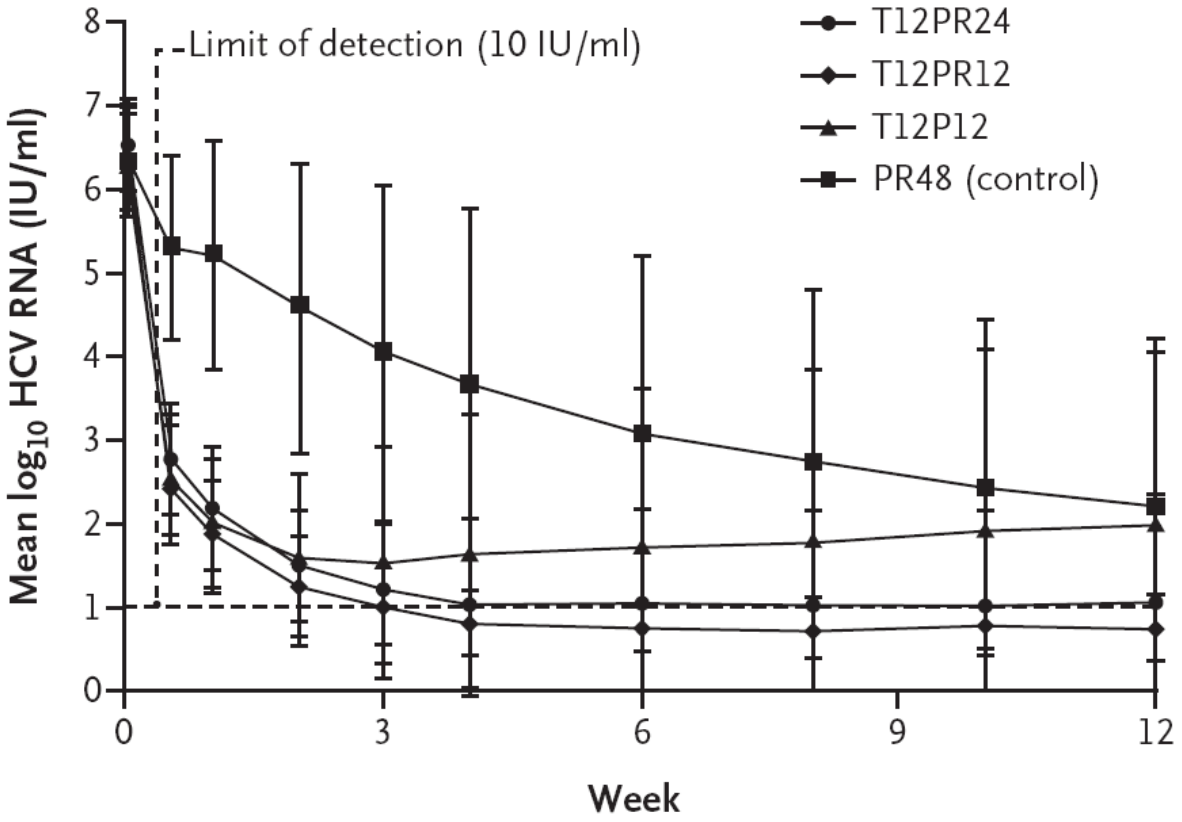


Sulkowski MS, et al. EASL 2012. Abstract 1162. Poster to be presented on Saturday 21st April

Is ribavirin reduction the best strategy? Effect on SVR?

Role of ribavirin in DAA combination: results from PROVE2 study

Herzode C et al. N Engl J Med 2009; 360:1839



No RBV

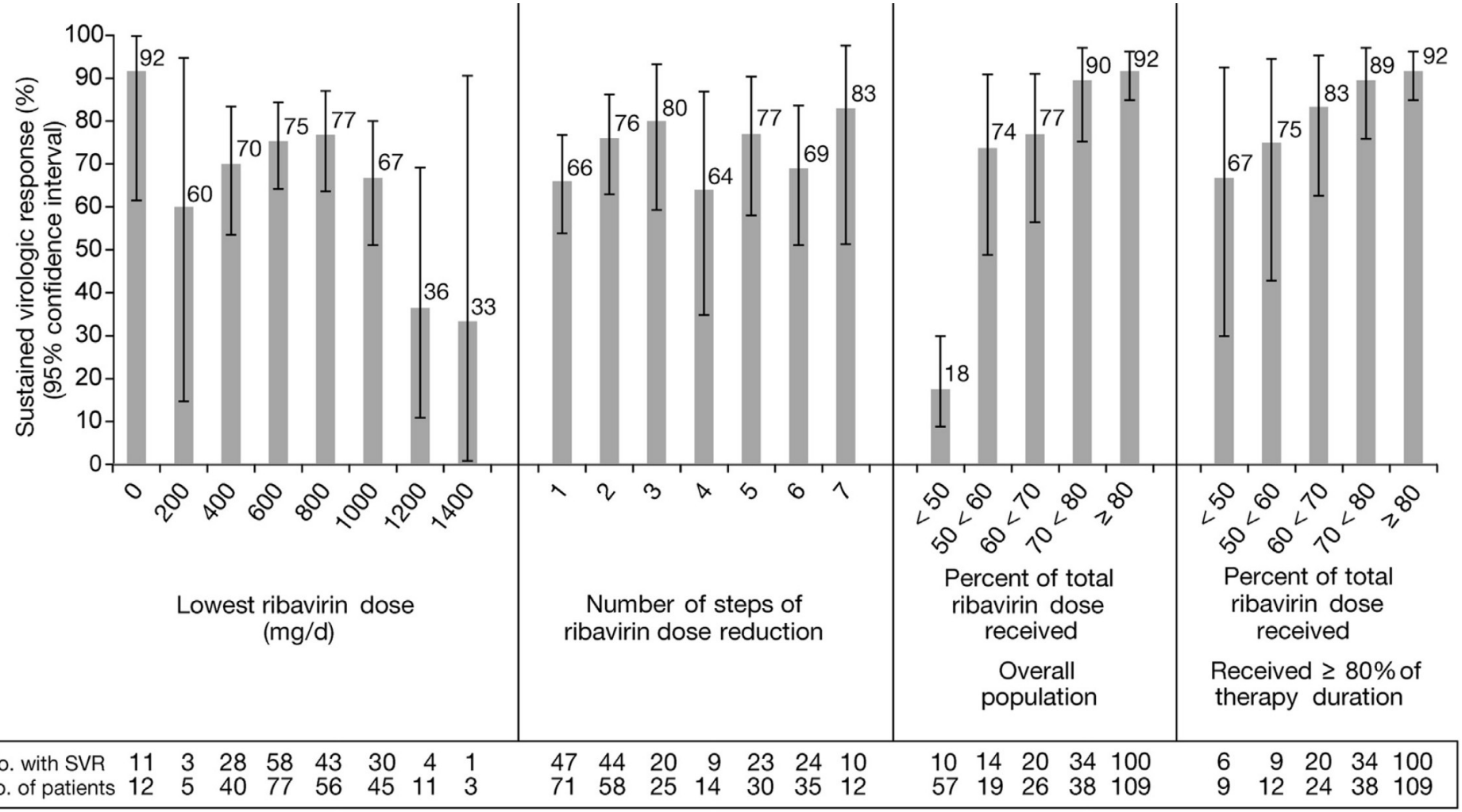
No. of Patients										
T12PR24	81	74	80	77	76	74	73	70	68	67
T12PR12	82	79	81	80	80	80	79	78	75	72
T12P12	78	72	78	74	74	73	73	72	70	70
PR48 (control)	82	78	80	80	79	79	78	77	77	77

Low dose ribavirin from the beginning?
High risk of breakthrough and relapse (SPRINT-1)

	Ribavirin dose (mg/d)	
	800-1400	400-1000
Relapse	3-7%	22%
Breakthrough	4-12%	27%

Kwo PY et al. Lancet 2010; 376:705

Management of anemia: Epo or RBV dose reduction?



No. with SVR	11	3	28	58	43	30	4	1	47	44	20	9	23	24	10	10	14	20	34	100	6	9	20	34	100
No. of patients	12	5	40	77	56	45	11	3	71	58	25	14	30	35	12	57	19	26	38	109	9	12	24	38	109

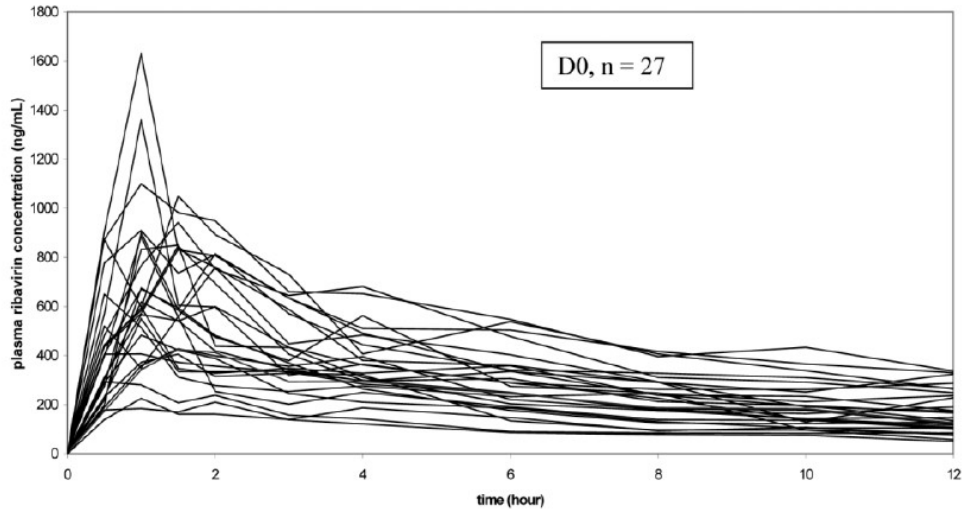
Poordad F et al. Gastroenterology 2013; 145: 1035

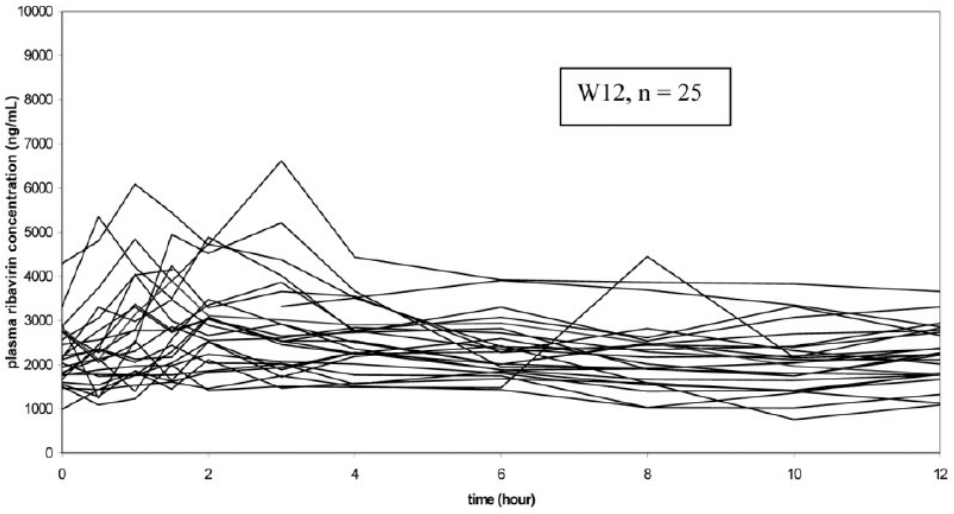
Higher SVR rates in anemic patients: No influence by EPO

SVR (%)

Sulkowksi M et al., AASLD 2008, Abstract 1851

Plasma ribavirin concentrations on day 0 and week 12

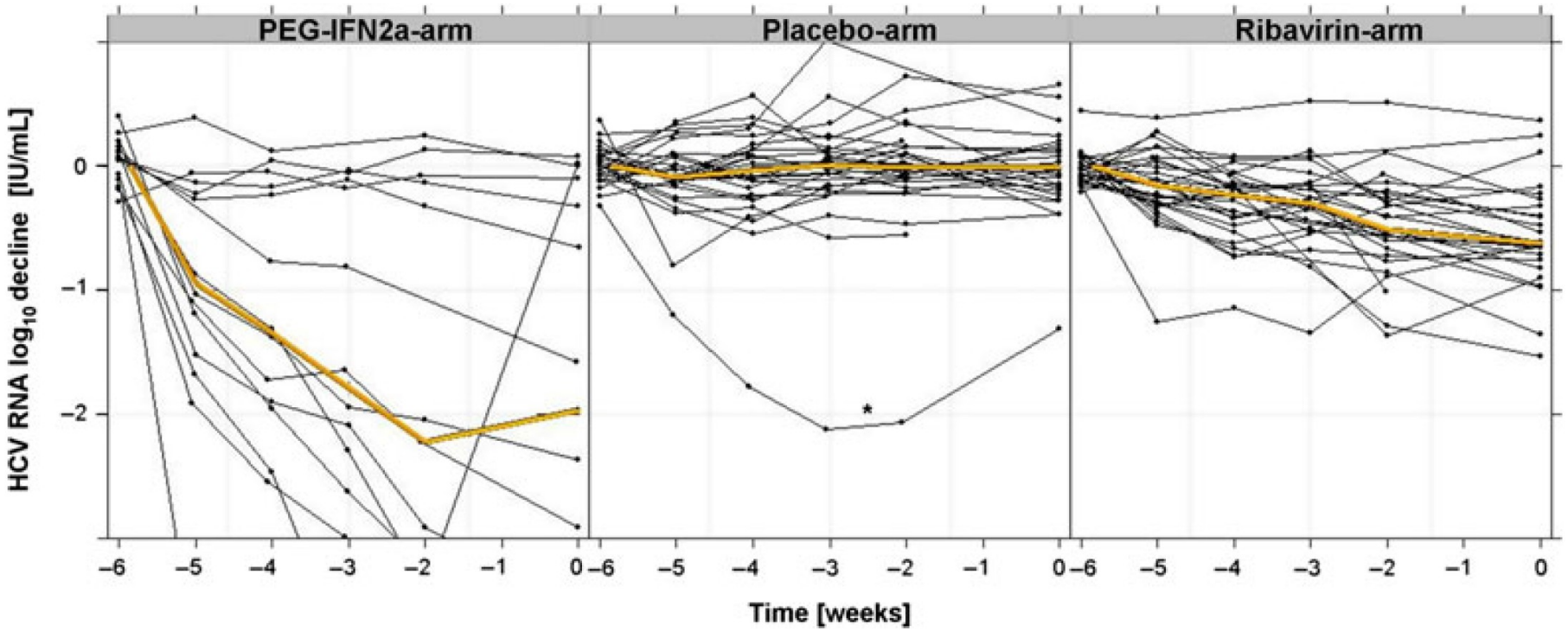




- Large interindividual variability of dose-concentration relationship
- No significant correlation between ribavirin AUC and weight-standardized dose
- Even at steady state (W12) RBV plasma concentrations showed large differences between T0 and T12h

Loustaud-Ratti V et al. Hepatology 2008; 47; 1453

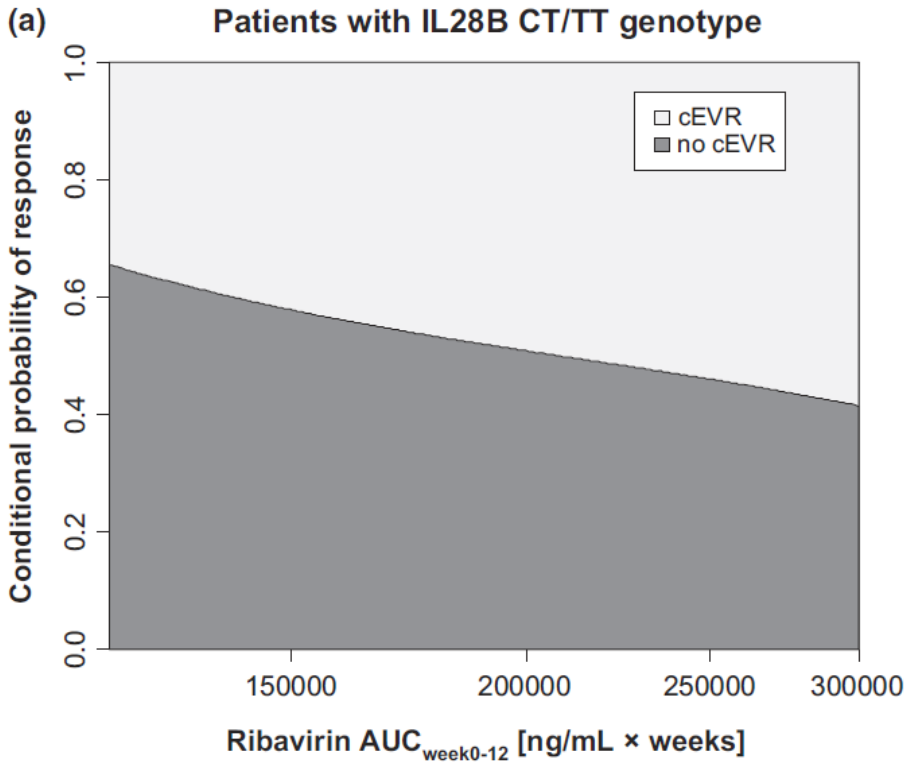
Antiviral mechanisms of ribavirin monotherapy

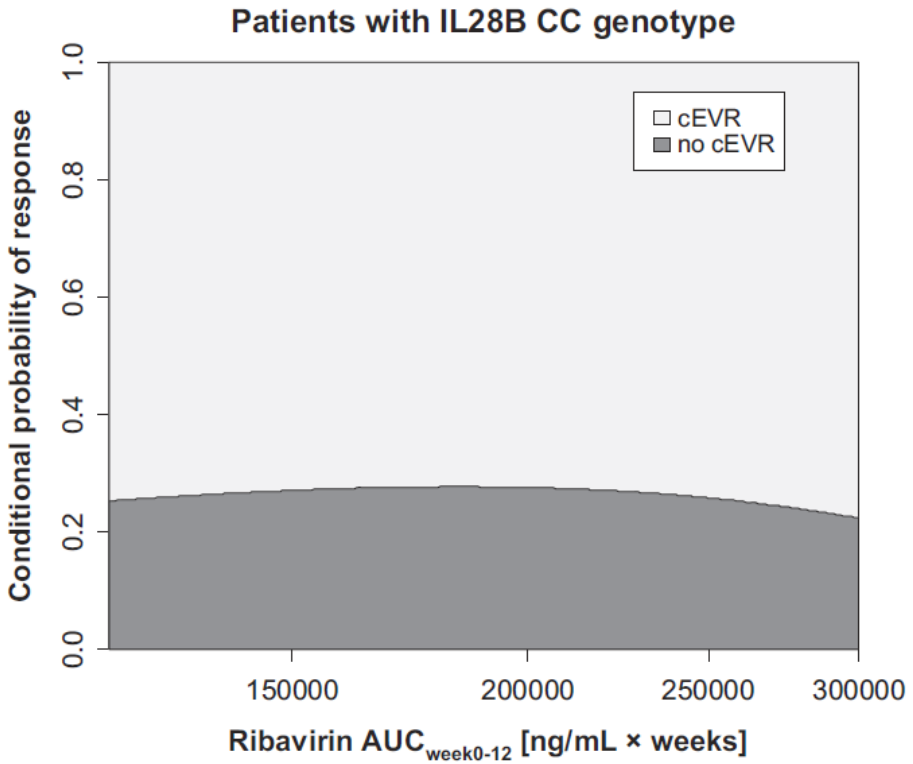


Mihm U et al. J Viral Hepat 2014; 21: 42

Antiviral mechanisms of ribavirin monotherapy

Week 12 virologic response (cEVR)

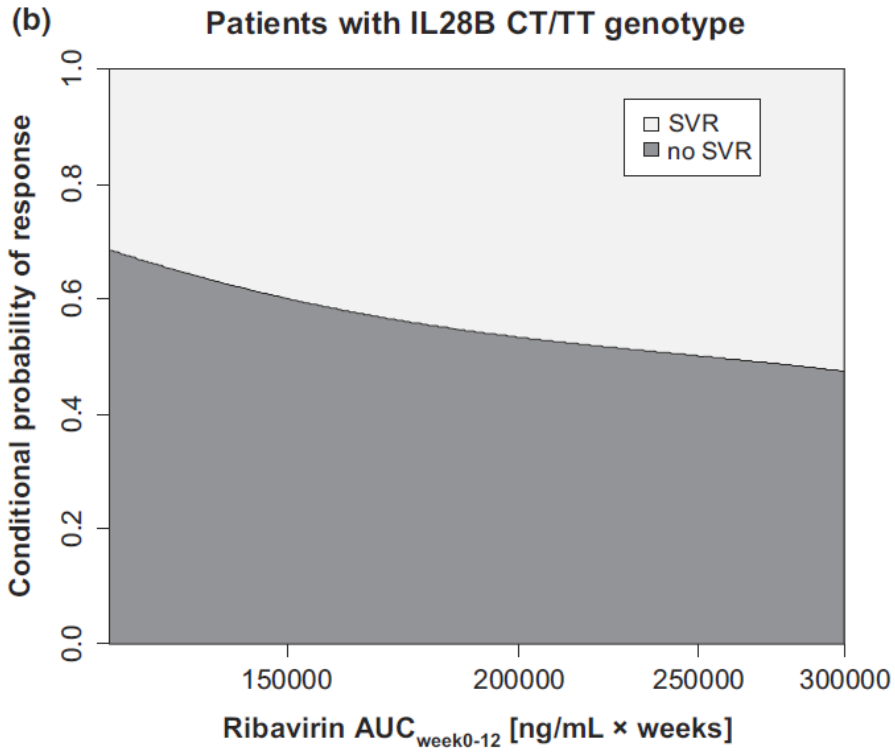


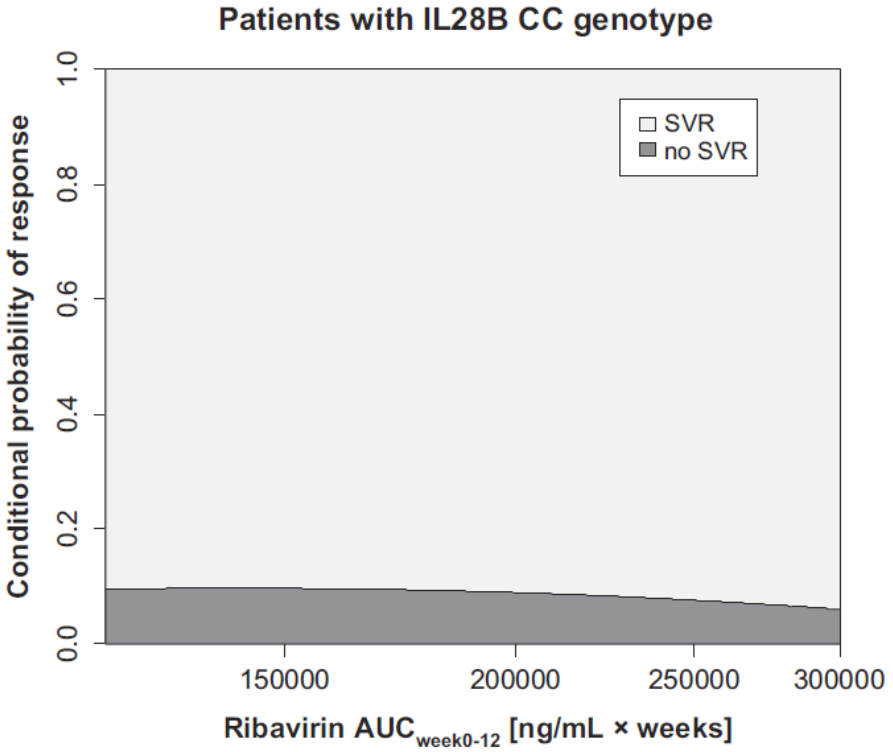


Mihm U et al. J Viral Hepat 2014; 21: 42

Antiviral mechanisms of ribavirin monotherapy

Sustained virologic response (SVR)

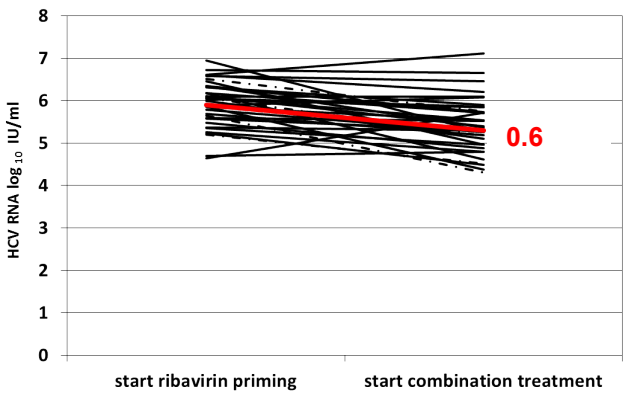




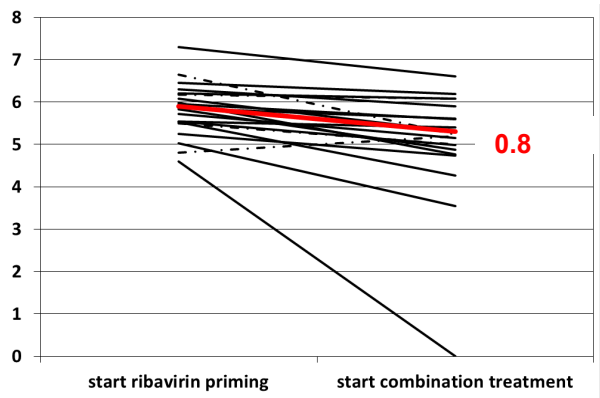
Mihm U et al. J Viral Hepat 2014; 21: 42

Antiviral effects of ribavirin monotherapy („priming“) in relation to prior response pattern

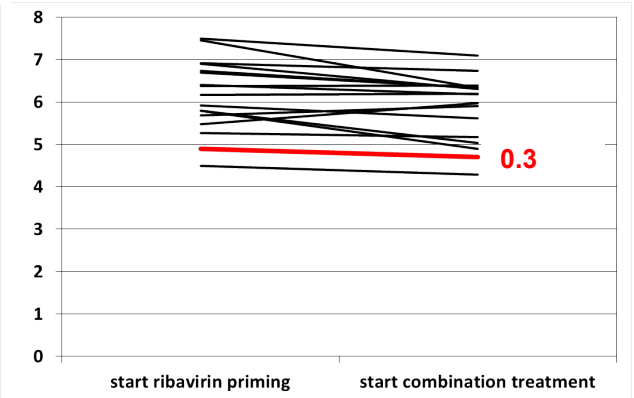
Treatment naive patients (n=37)



patients with prior relapse (n=20)))

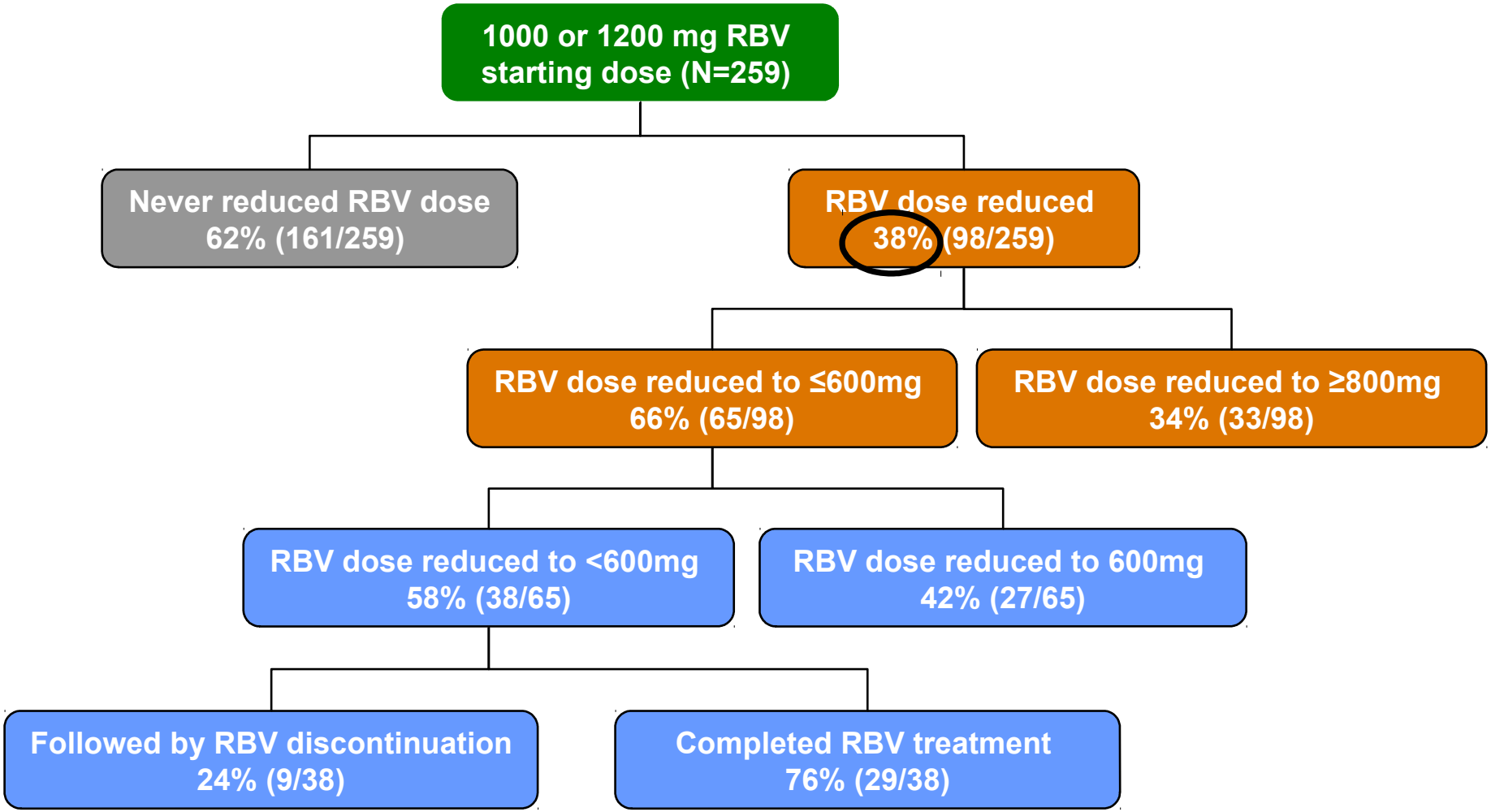


Prior patients with prior non response (n=16)



Fülöp B et al. EASL 2012

Ribavirin dose reduction during telaprevir triple therapy in *pre-treated* patients



REALIZE (T12PR48), N=259

Sulkowski MS, et al. J Hepatol 2012;56 (Suppl 2):S459–S460

Ribavirin dose reduction during TVR Triple and early virologic response patterns

(Treatment experienced pts with advanced fibrosis, N=205, HCV type 1)

	Ribavirin dose reduction		
	W0-W4	W4-W12	No
cEVR	59%	83%	88%
cEVR in Nulls	44%	75%	ND
cEVR in Hb < 12 g/dL vs. > 12 g/dL on-treatment: 86% vs. 66%			

*EVR = early virologic response at week 12

Janczewska E et al. J Hepatol 2013 (Suppl) S342; #816 (poster, EASL 2013)

Anemia management
Summary

Summary: anemia in first generation protease-inhibitor-based triple therapy

Key Points 1

In the registration trials, triple therapy with boceprevir or telaprevir was associated with an increase in the incidence and severity of anemia in comparisons with PegIFN plus ribavirin

Key Points 2

The incidence of anemia is even greater in real practice cohorts, especially in advanced fibrosis and in transplanted patients

Key Points 3

Age, female gender, low baseline hemoglobin and cirrhosis are the main factors associated with higher incidence of anemia during triple therapy

Romero-Gomez M et al. J Hepatol 2013; 59: 1323

Summary: anemia in first generation protease-inhibitor-based triple therapy

Key Points 4

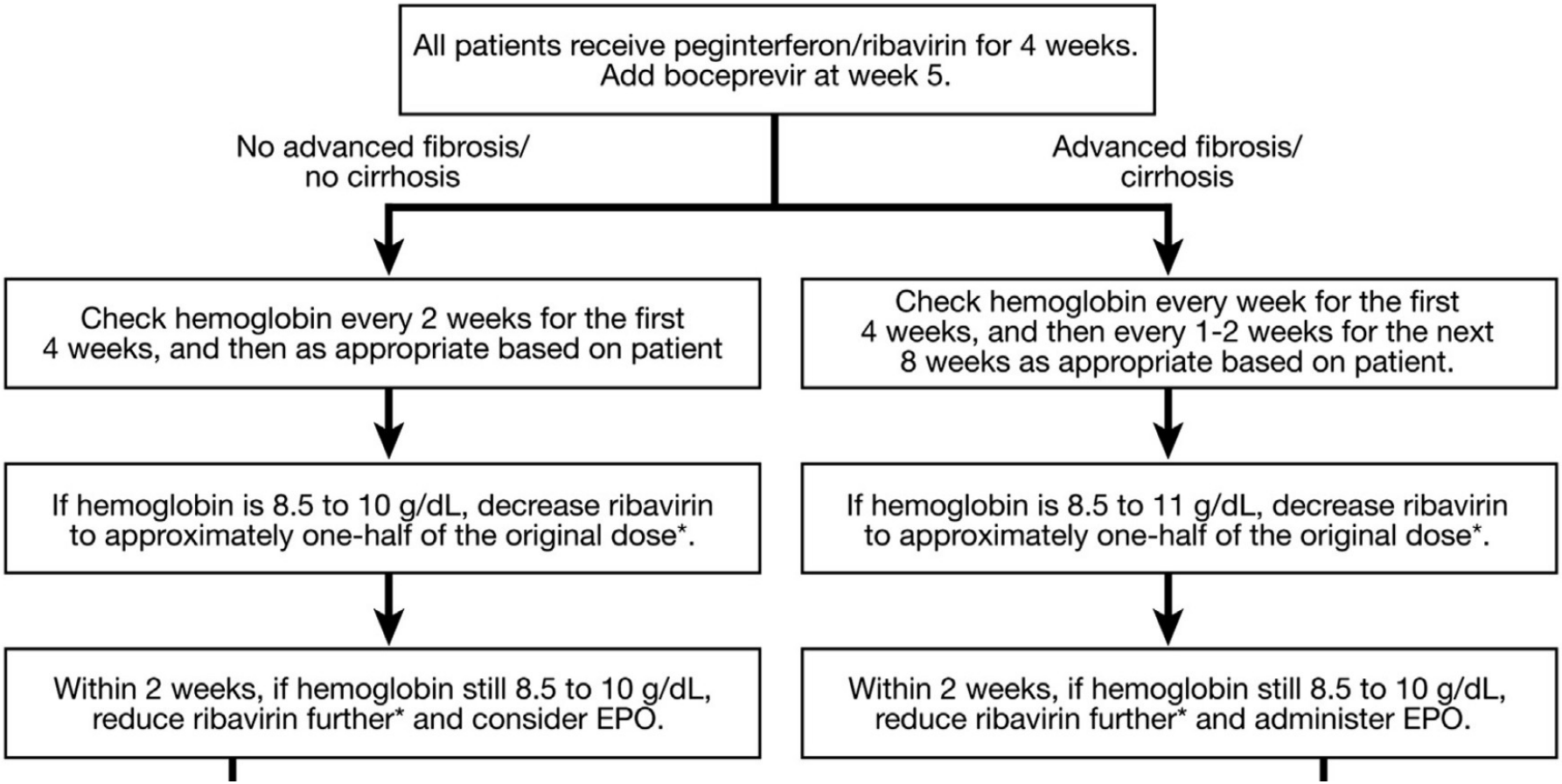
Ribavirin dose reduction should be the preferred first strategy for anemia management. Epoetin belongs to the second line and pack red blood transfusion are eventually needed in a subgroup of patients

Key Points 5

The reduction of ribavirin does not adversely impact the ultimate SVR rate. This information is not very robust in difficult-to-cure patients, especially in patients with cirrhosis

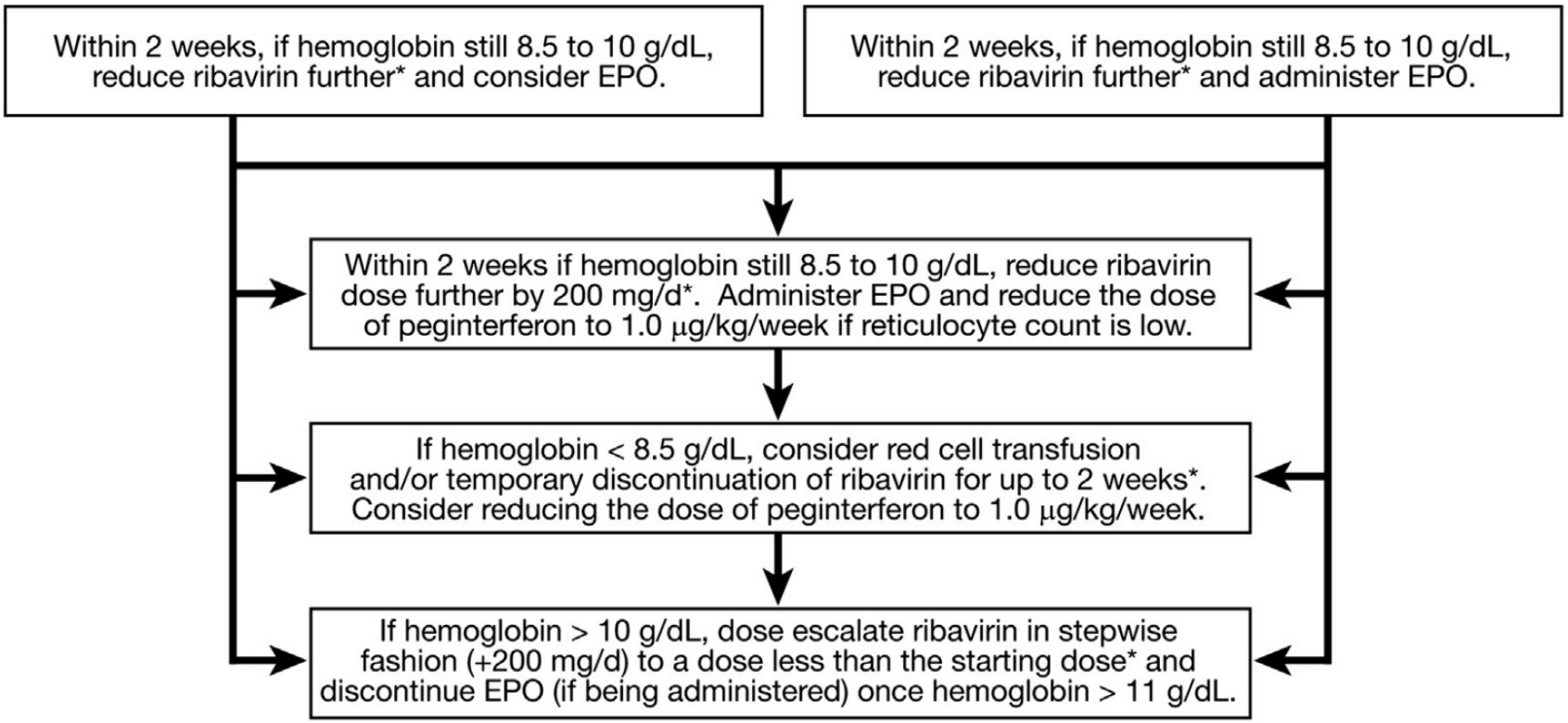
Romero-Gomez M et al. J Hepatol 2013; 59: 1323

Proposed algorithm for the management of boceprevir-related anemia



Poordad F et al. Gastroenterology 2013; 145: 1035

Proposed algorithm for the management of boceprevir-related anemia



*The total mg of ribavirin received by the patient over the total treatment duration should be 50% or greater of the total intended mg of ribavirin based on the starting mg of ribavirin per day and the days of treatment based on response-guided therapy.

Poordad F et al. Gastroenterology 2013; 145: 1035

Risks of EPO?

- On May 9, 2007, the U.S. Food and Drug Administration included a new ***black box warning***
- advising physicians to adjust the ESA dose to maintain the lowest hemoglobin level needed to avoid the need for a blood transfusion.
- physicians and patients were to weigh the risks of ESAs against the risks of a blood transfusion.
- recent studies suggested they might cause thromboembolic events and increase the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL

ESA = Erythropoiesis-stimulating agents

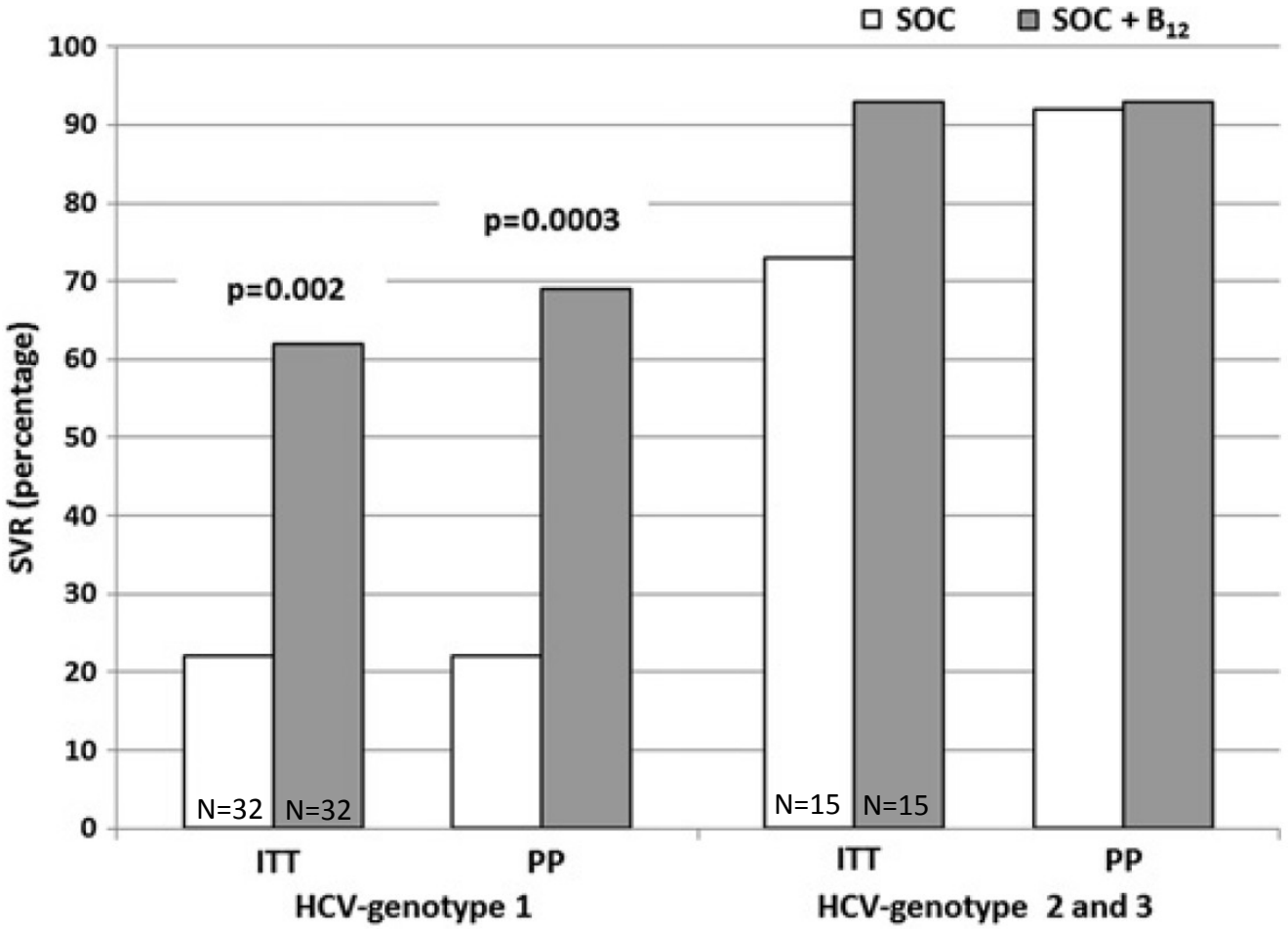
Steinbrook R. N Engl J Med 2007; 356:2448

Erythropoietin: side effects?

	On or after erythropoietin (n = 295)	No erythropoietin (n = 392)
Patients reporting any thromboembolic adverse event[b]	9 (3.1)	1 (0.3)
Pulmonary embolism	1 (<1)	1 (<1)
Thrombosed varicose vein	2 (<1)	0 (0)
Acute myocardial infarction	1 (<1)	0 (0)
Arterial occlusive disease	1 (<1)	0 (0)
Arteriosclerosis	1 (<1)	0 (0)
Cerebrovascular accident	1 (<1)	0 (0)
Deep vein thrombosis	1 (<1)	0 (0)
Thrombophlebitis superficial	1 (<1)	0 (0)
Transient ischemia attack	1 (<1)	0 (0)
Venous thrombosis	1 (<1)	0 (0)

Poordad F et al. Gastroenterology 2013; 145: 1035

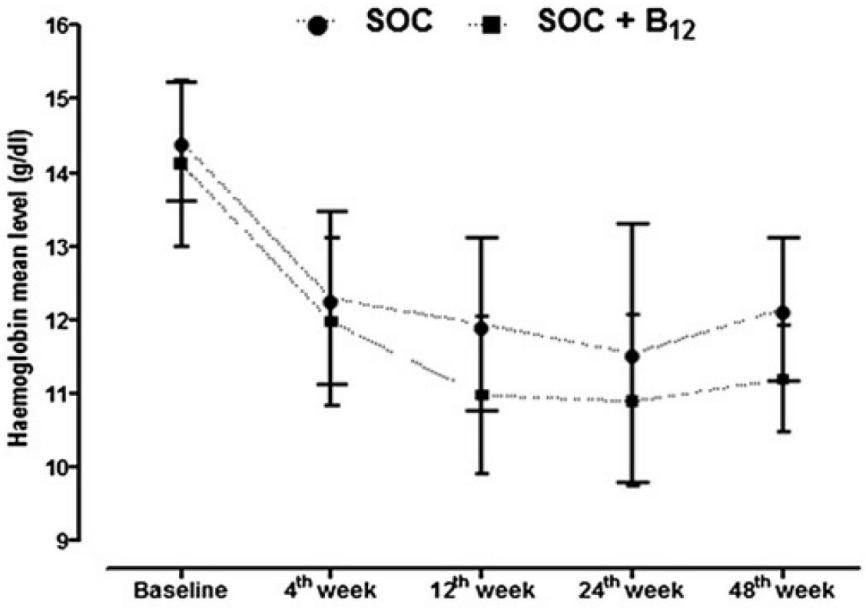
Vitamin B12 supplementation in dual antiviral therapy: effect on SVR

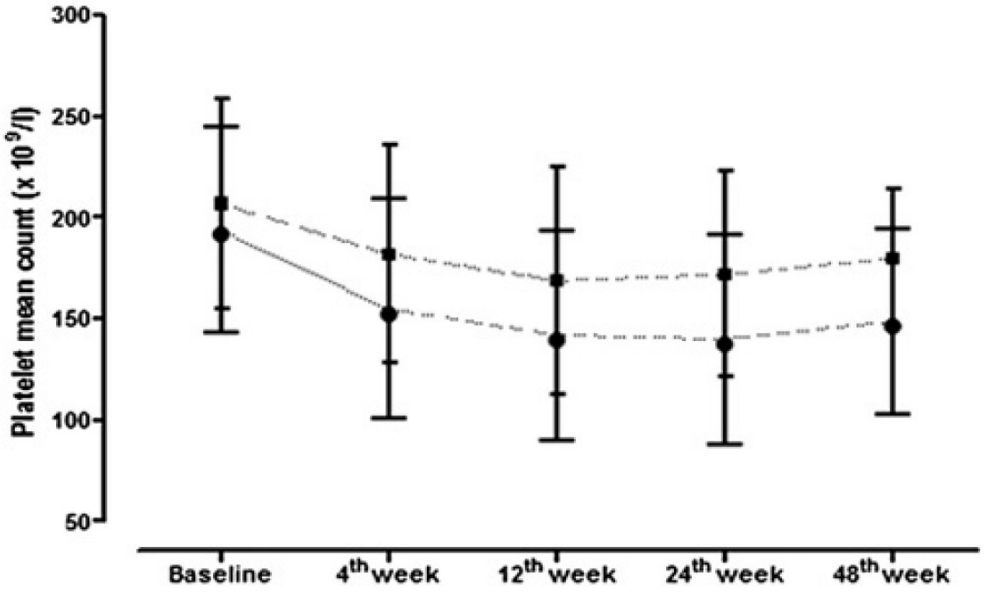


Vitamin B12: 5000 µg intramuscular injection every 4 weeks during treatment

Rocco A et al. Gut 2012

Vitamin B12 supplementation in dual antiviral therapy: effect on hemoglobin and platelet levels



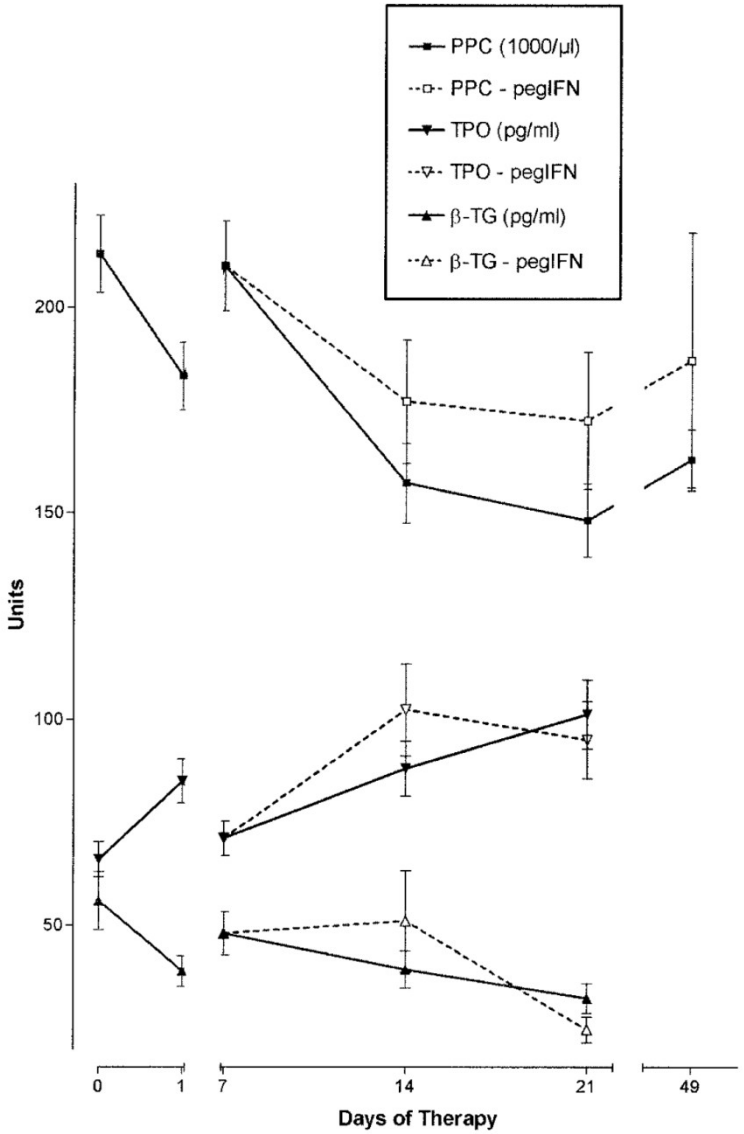


Vitamin B12: 5000 µg intramuscular injection every 4 weeks during treatment

Rocco A et al. Gut 2012

Thrombocytopenia

Peripheral platelet counts during interferon-based treatment



Peck-Radosavljevic M et al. Gastroenterology 2002;123:141

Telaprevir (REALIZE): laboratory abnormalities

n (%)	Cirrhotics (F4) N=139	Non-cirrhotics (F0–3) N=391
Hemoglobin		
≤10g/dL	63 (46)	156 (40)
≤8.5g/dL	19 (14)	49 (13)
Neutrophils		
Grade 3 (500 to <750/mm3)	35 (25)	68 (17)
Grade 4 (<500/mm3)	10 (7)	9 (2)
Grade 3/4	45 (32)	77 (19)
Platelets		
Grade 3 (25,000 to <50,000/mm3)	16 (12)	12 (3)
Grade 4 (<25,000/mm3)	2 (1)	1 (<1)
Grade 3/4	18 (13)	13 (3)

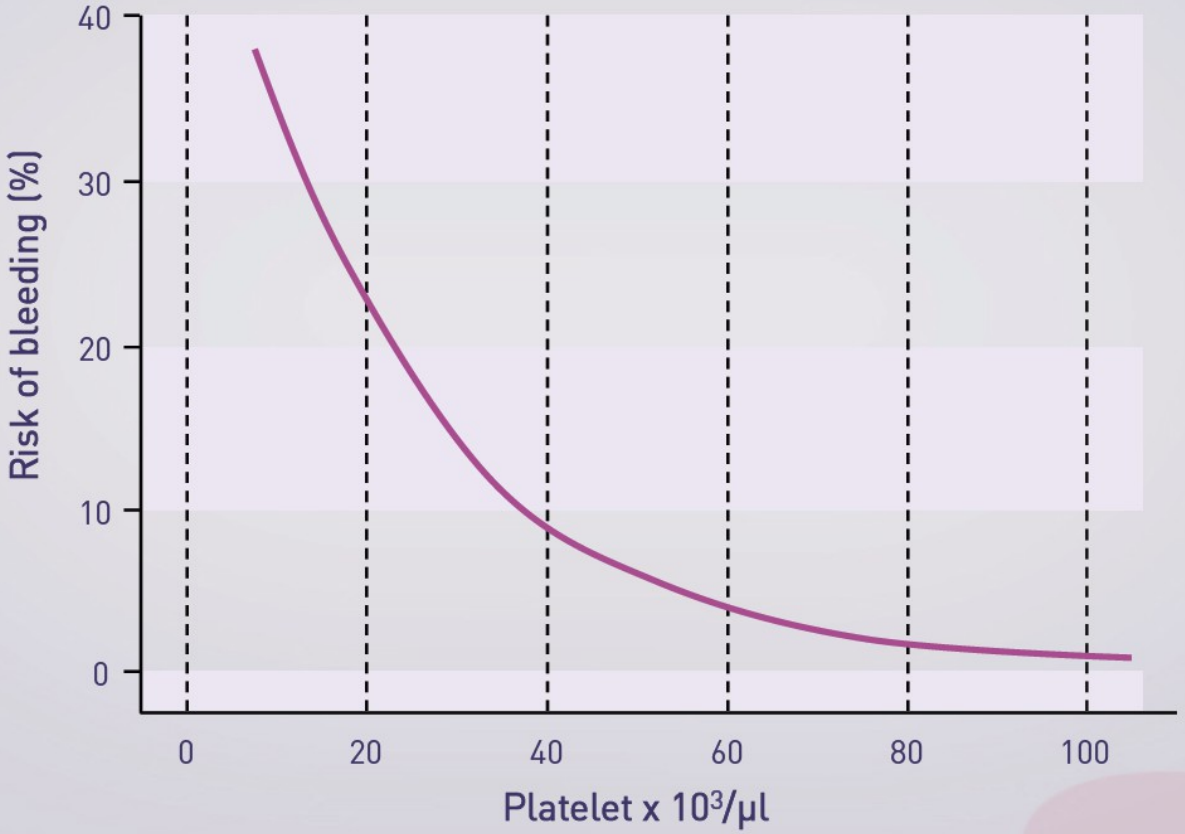
Pol S, et al. Hepatology 2011;54(Suppl. S1): Abstract 31

Risk of bleeding

High risk of bleeding in severely thrombocytopenic patients undergoing hepatitis C treatment

321 chronic hepatitis C patients with genotype 1-4 (21% cirrhotic) receiving pIFN/RBV.
Mean baseline platelet count = 191Gi/L

Risk of bleeding according to platelet count during antiviral therapy



Roomer R et al. *J Hepatol* 2010;53:455-459.

How to manage thrombocytopenia?

How to manage thrombocytopenia in 2012?

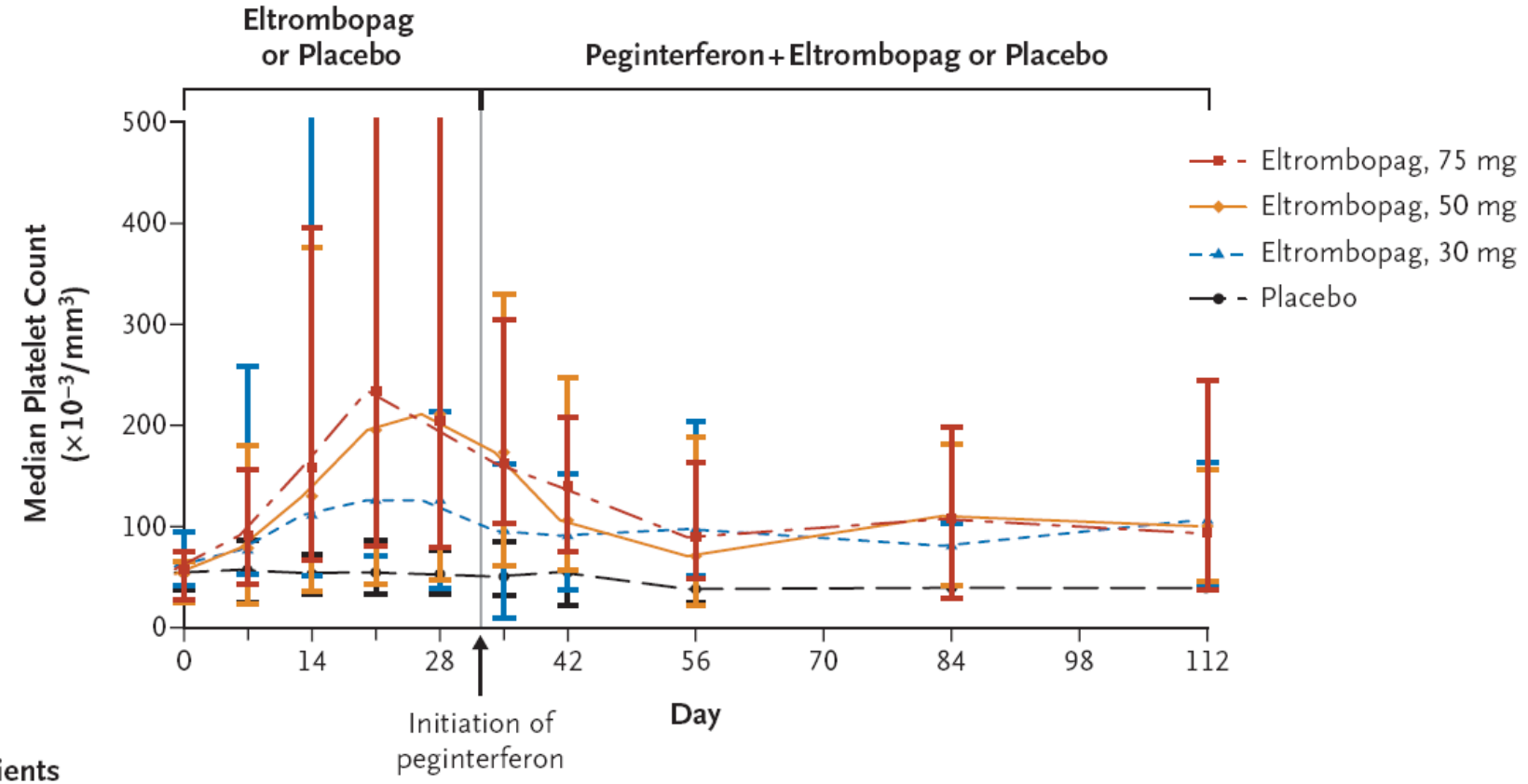
PegInterferon dose reduction if platelets < 30-50/nL

Try to maintain levels above 25/nL

Stop IFNa if platelets below 25/nL

Eltrombopag for HCV-associated thrombocytopenia

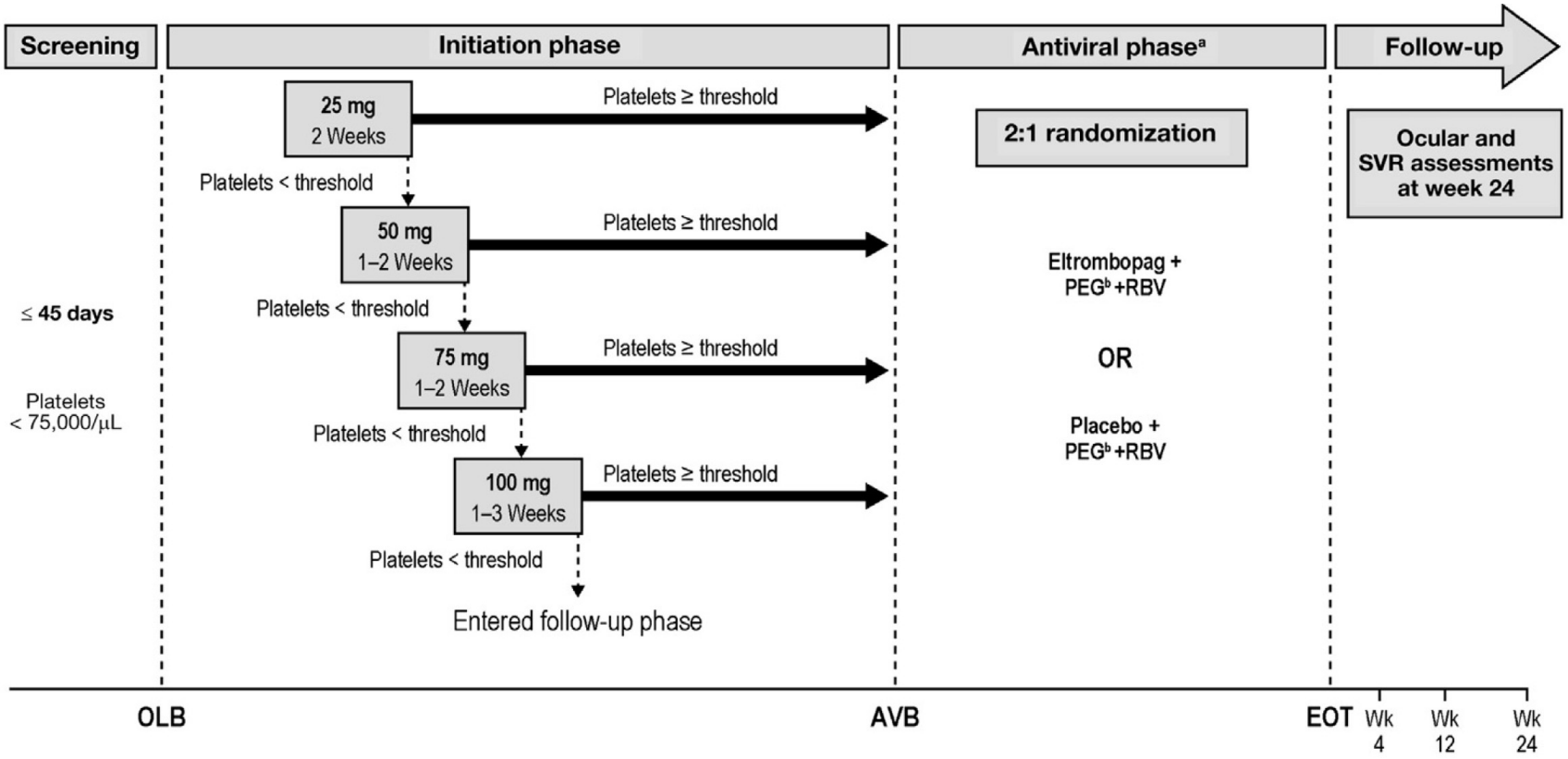
McHutchison JG et al. N Engl J Med 2007; 357: 2227



No. of Patients										
Placebo	18	18	18	17	14	3	3	4	2	1
Eltrombopag, 30 mg	14	14	14	12	11	10	10	9	7	6
Eltrombopag, 50 mg	19	19	17	16	15	12	14	12	10	10
Eltrombopag, 75 mg	23	23	22	22	20	18	20	18	17	15

Eltrombopag for treatment of thrombocytopenia in patients with HCV cirrhosis

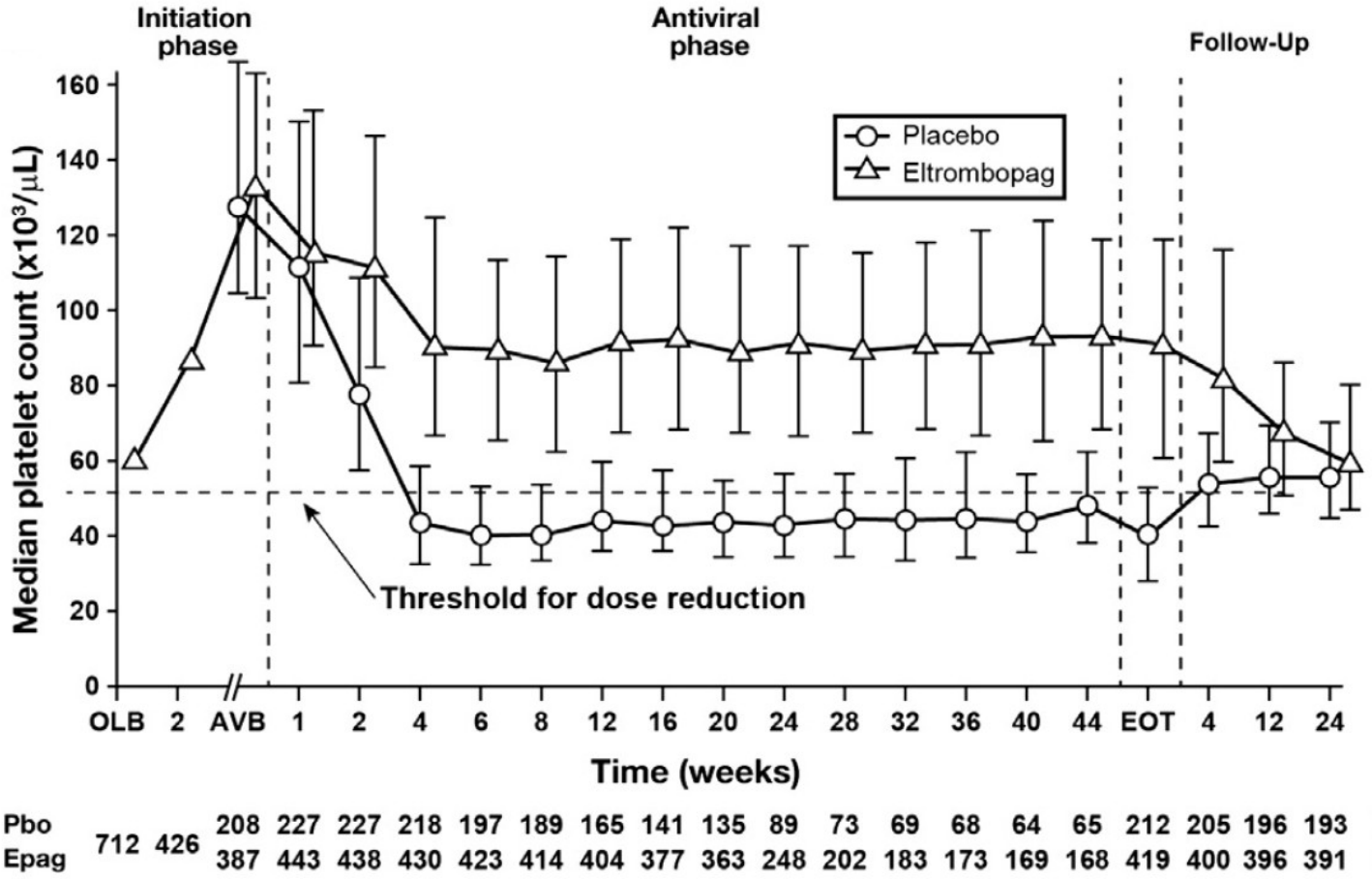
ENALBE-1 (n=715) + ENALBLE-2 (n=805)



Afdahl NH et al. Gastroenterology 2014

Eltrombopag for treatment of thrombocytopenia in patients with HCV cirrhosis

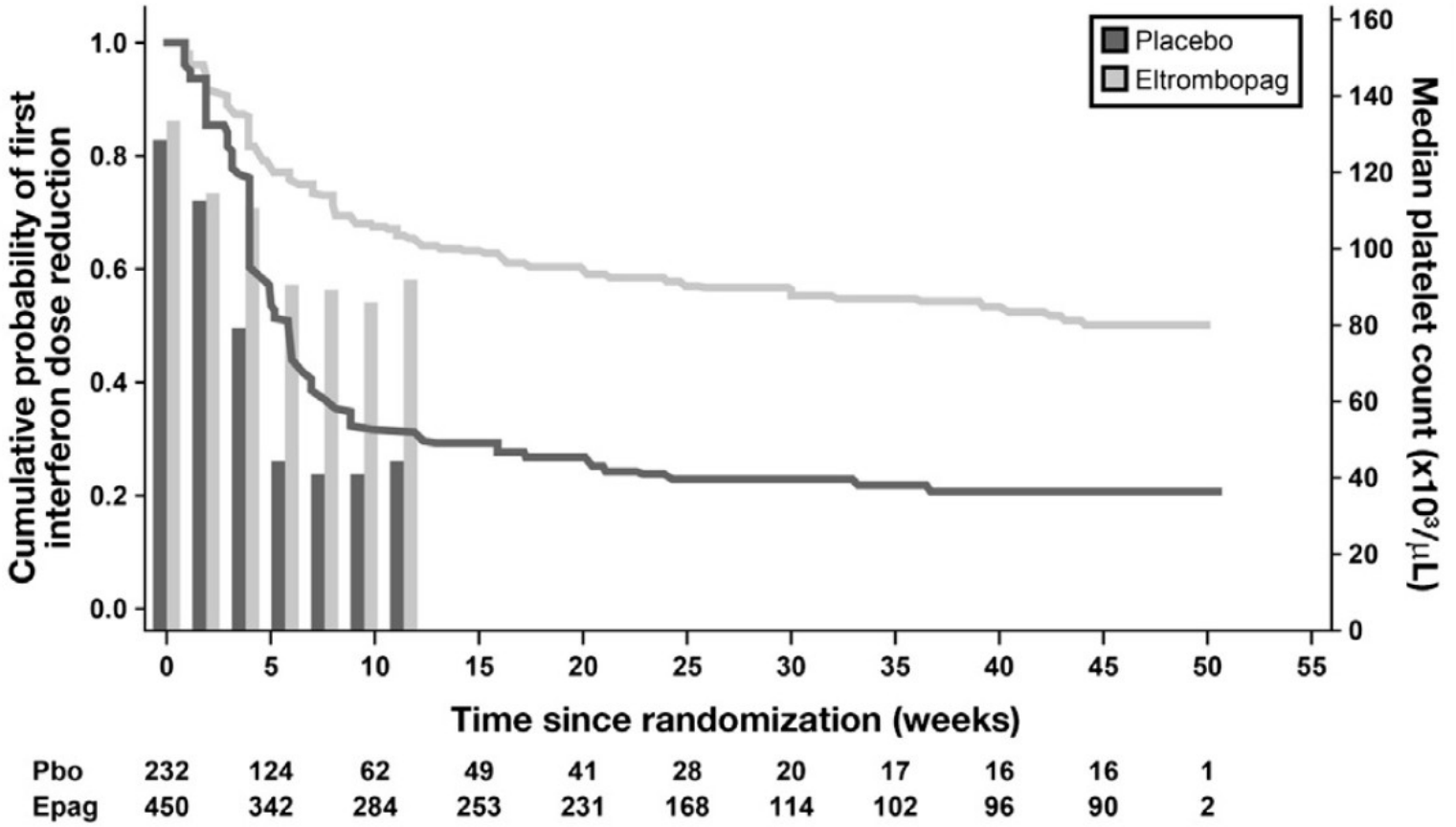
ENALBE-1 (n=715; Peg-IFNa-2a)



Afdahl NH et al. Gastroenterology 2014

Eltrombopag for treatment of thrombocytopenia in patients with HCV cirrhosis

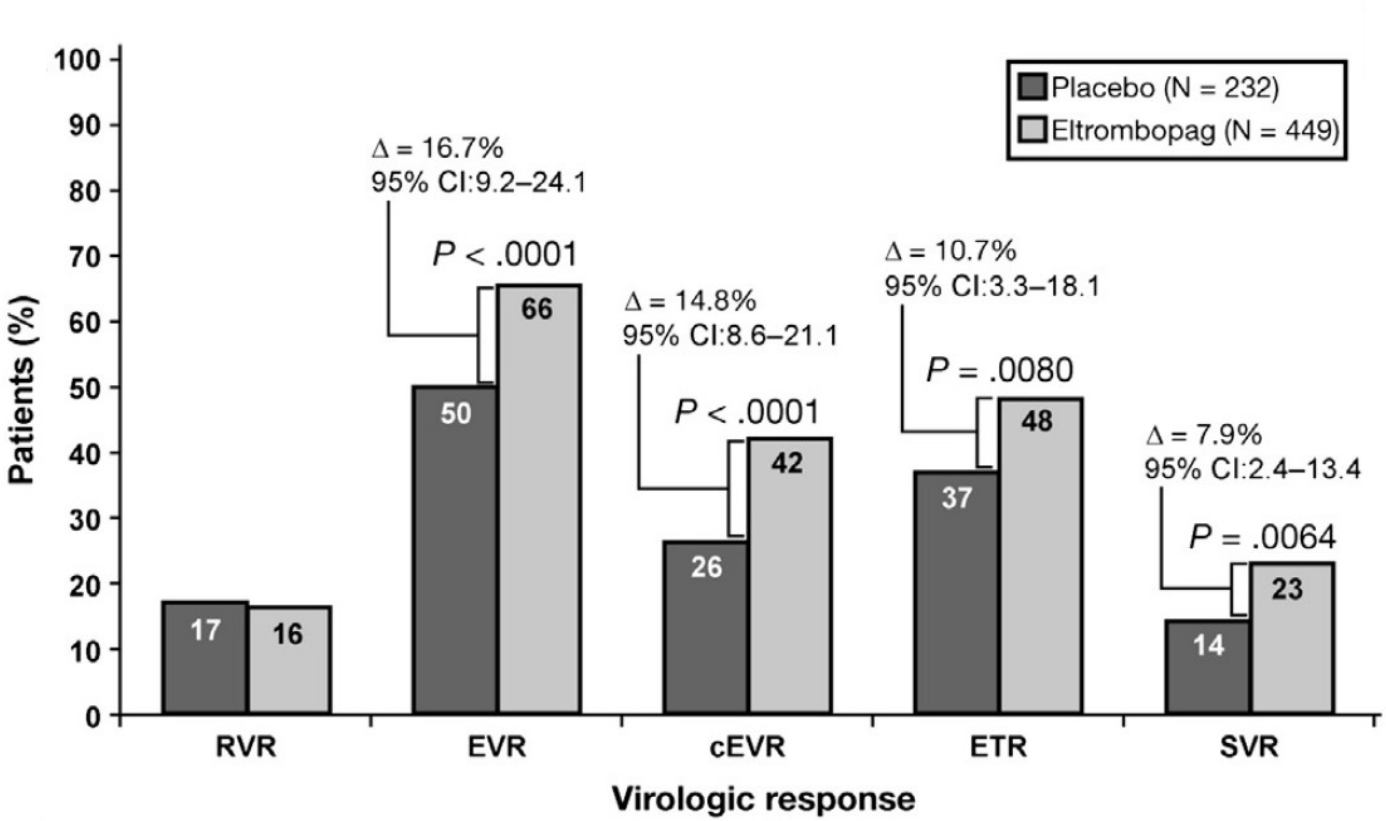
ENALBE-1 (n=715; Peg-IFNa-2a)



Afdahl NH et al. Gastroenterology 2014

Eltrombopag for treatment of thrombocytopenia in patients with HCV cirrhosis

ENALBE-1 (n=715; Peg-IFNa-2a)



Afdahl NH et al. Gastroenterology 2014

Eltrombopag for treatment of thrombocytopenia in patients with HCV cirrhosis

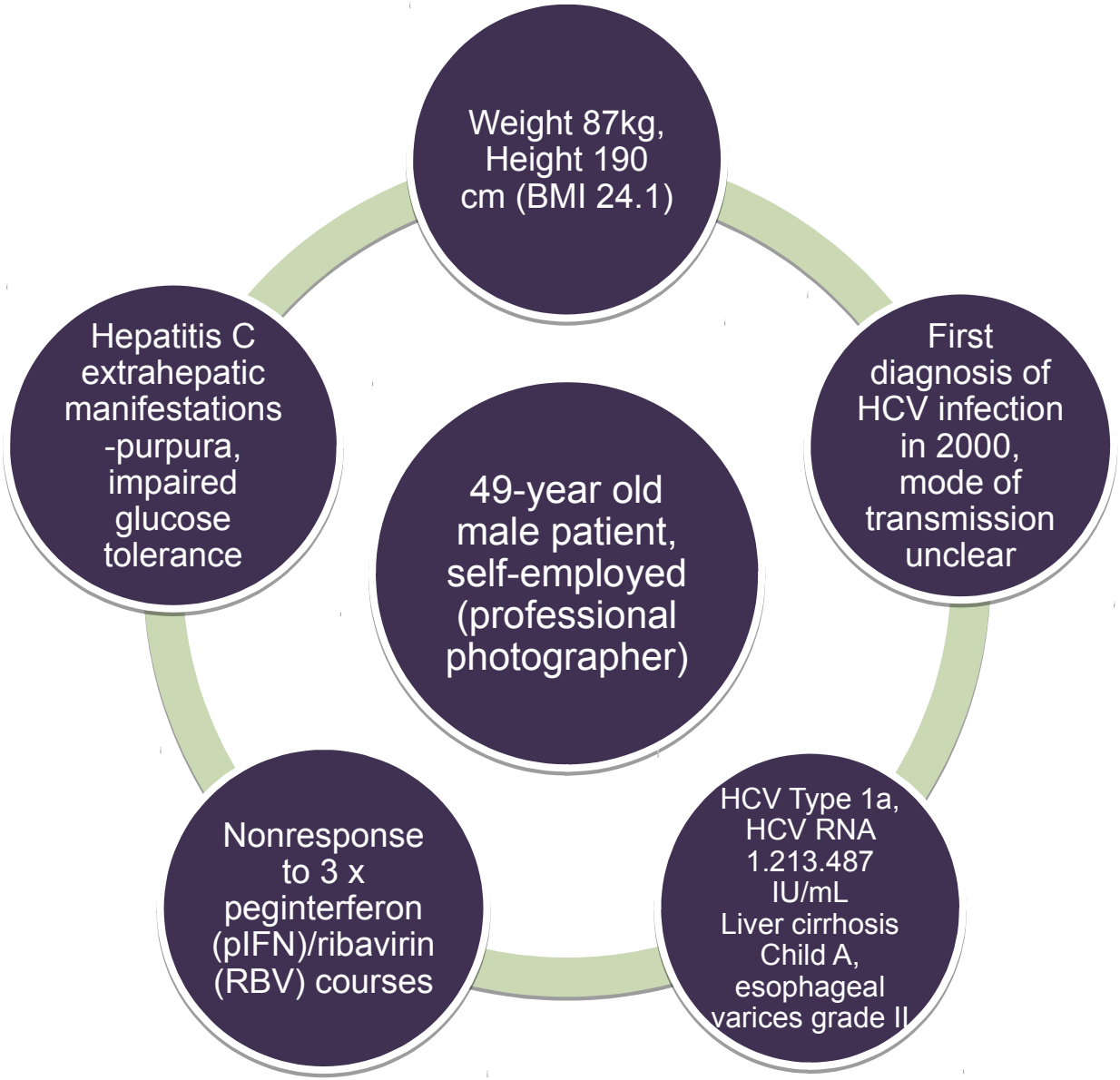
ENALBE-1 + -2

Table 3. Thromboembolic Events During the Antiviral Phase

	ENABLE-1		ENABLE-2	
	Eltrombopag (n = 449)	Placebo (n = 232)	Eltrombopag (n = 506)	Placebo (n = 252)
Number of events, n (%)	12	4	22	1
Serious	3 (1)	2 (1)	9 (2)	0
Leading to withdrawal from study	0	1 (<1)	7 (1)	0
DAIDS grade 3/grade 4	6 (1)	2 (1)	14 (3)	0
Number of patients with event, n (%)	11 (2)	4 (2)	20 (4)	1 (<1)
Portal venous thromboses	5 (1)	2 (1)	7 (1)	0
Deep venous thromboses	1 (<1)	0	5 (1)	0
Thrombosis	2 (<1)	0	1 (<1)	0
Acute myocardial infarction	1 (<1)	0	1 (<1)	0
Angina unstable	0	1 (<1)	1 (<1)	0
Ischemic stroke	1 (<1)	0	1 (<1)	0
Retinal vascular disorder	2 (<1)	1 (<1)	4 (1)	1 (<1)
Pulmonary embolism	-	-	1 (<1)	0
Femoral artery occlusion	-	-	1 (<1)	0
Outcome of events, n (%)[a]				
Recovered/resolved	6 (55)	2 (50)	12 (60)	1 (100)
Fatal	0	1 (25)	2 (10)	0

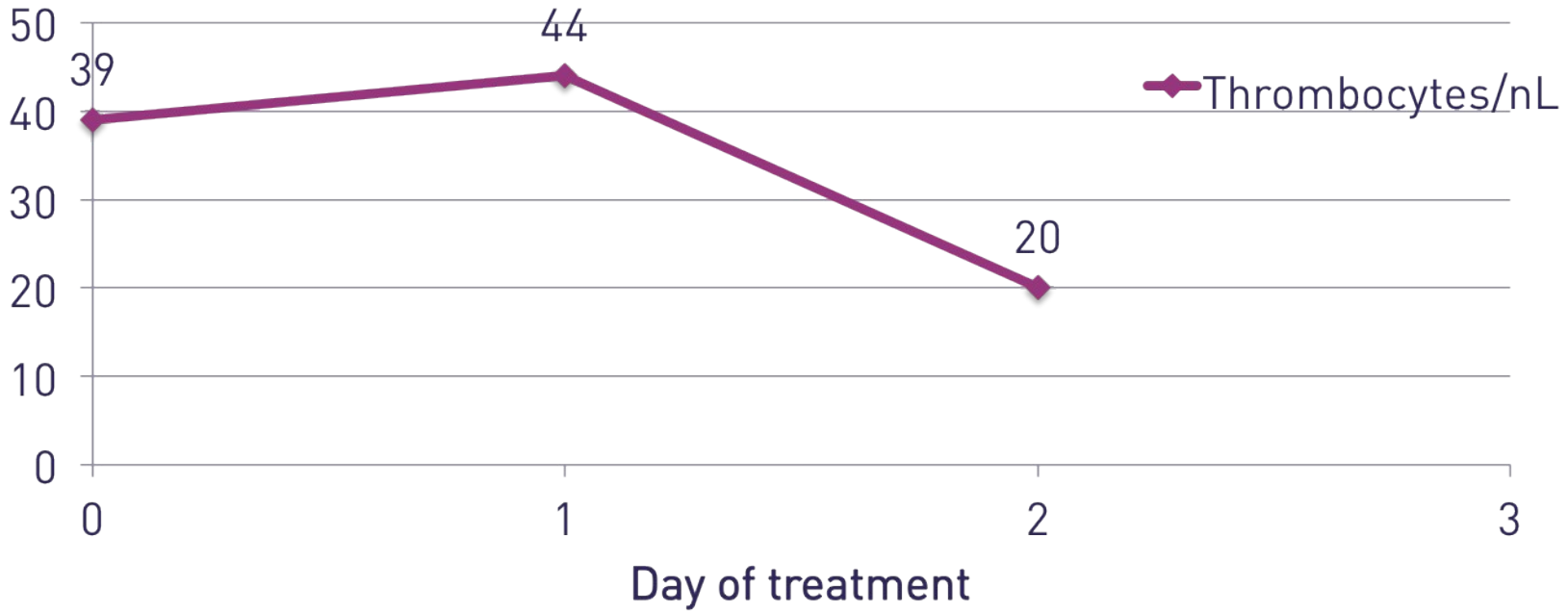
Afdahl NH et al. Gastroenterology 2014

Case 1: History



Case 1: Platelet counts on TVR triple

- Rapid decline of platelets at day 2 to 20/nl



Case 1: Platelet counts on TVR triple

- Rapid decline of platelets at day 2 to 20/nL
- Eltrombopag 50mg/day initiated