How to optimize current therapy of HCV genotype 1 infection with Boceprevir

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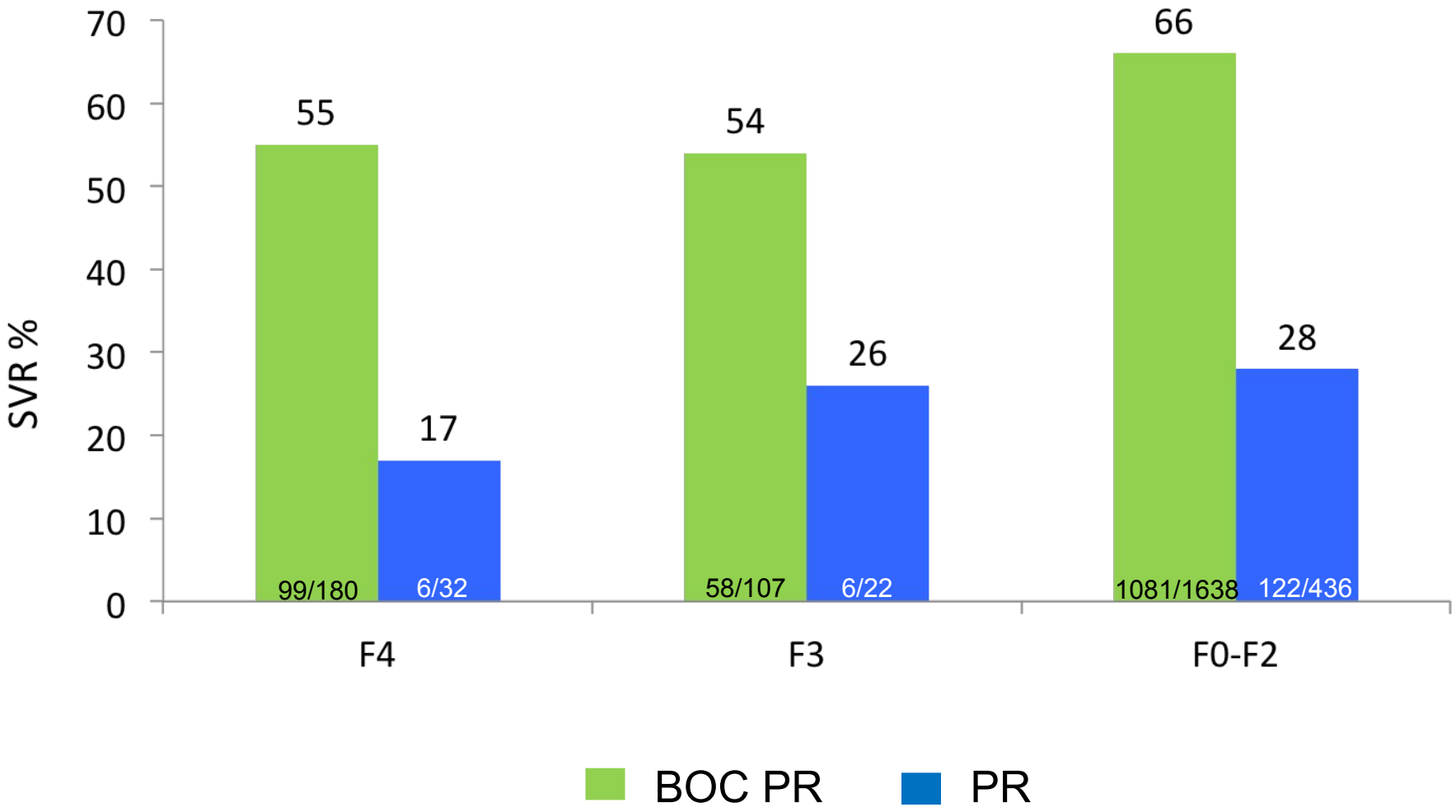
Disclosures

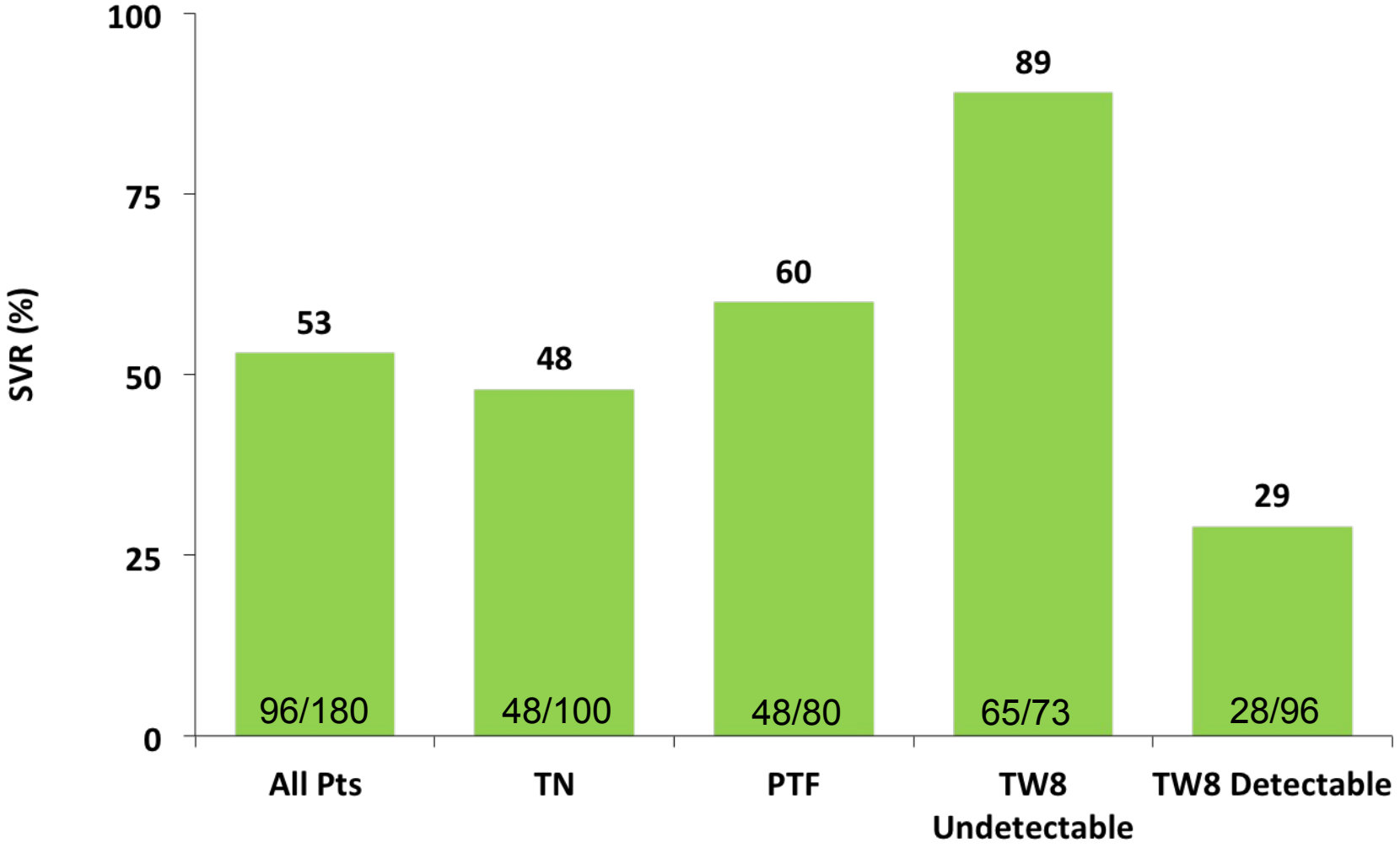
- Board member for : Schering-Plough, Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, Abbott, GSK, Vertex
- Speaker for : Roche, Schering-Plough, Merck, Janssen, Gilead, BMS, Abbvie

Meta-analysis of five Phase 3 clinical trials with Boceprevir



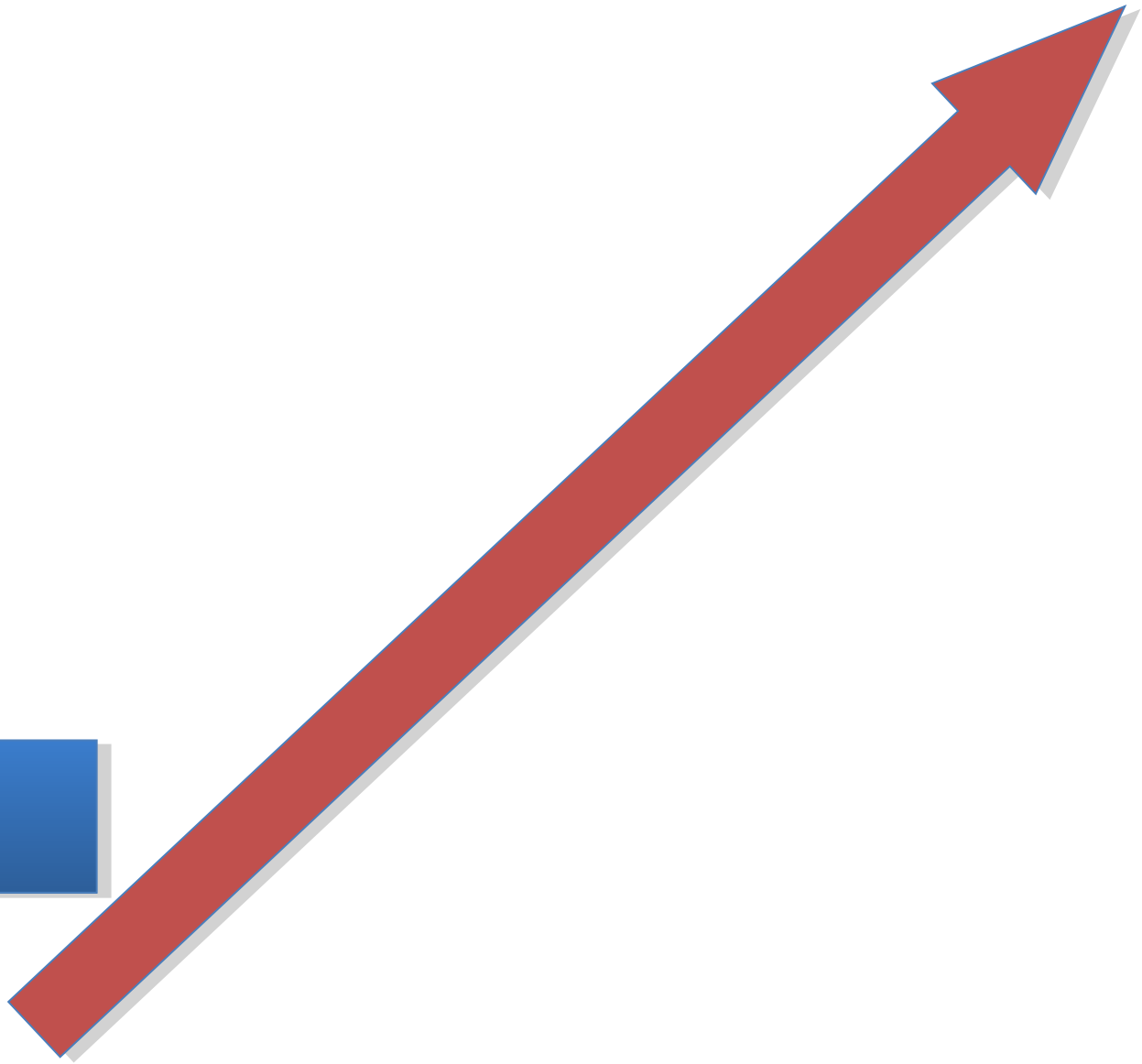
Vierling JM, et al. EASL 2013

Response to BOC/PR in F4 Patient Subgroups



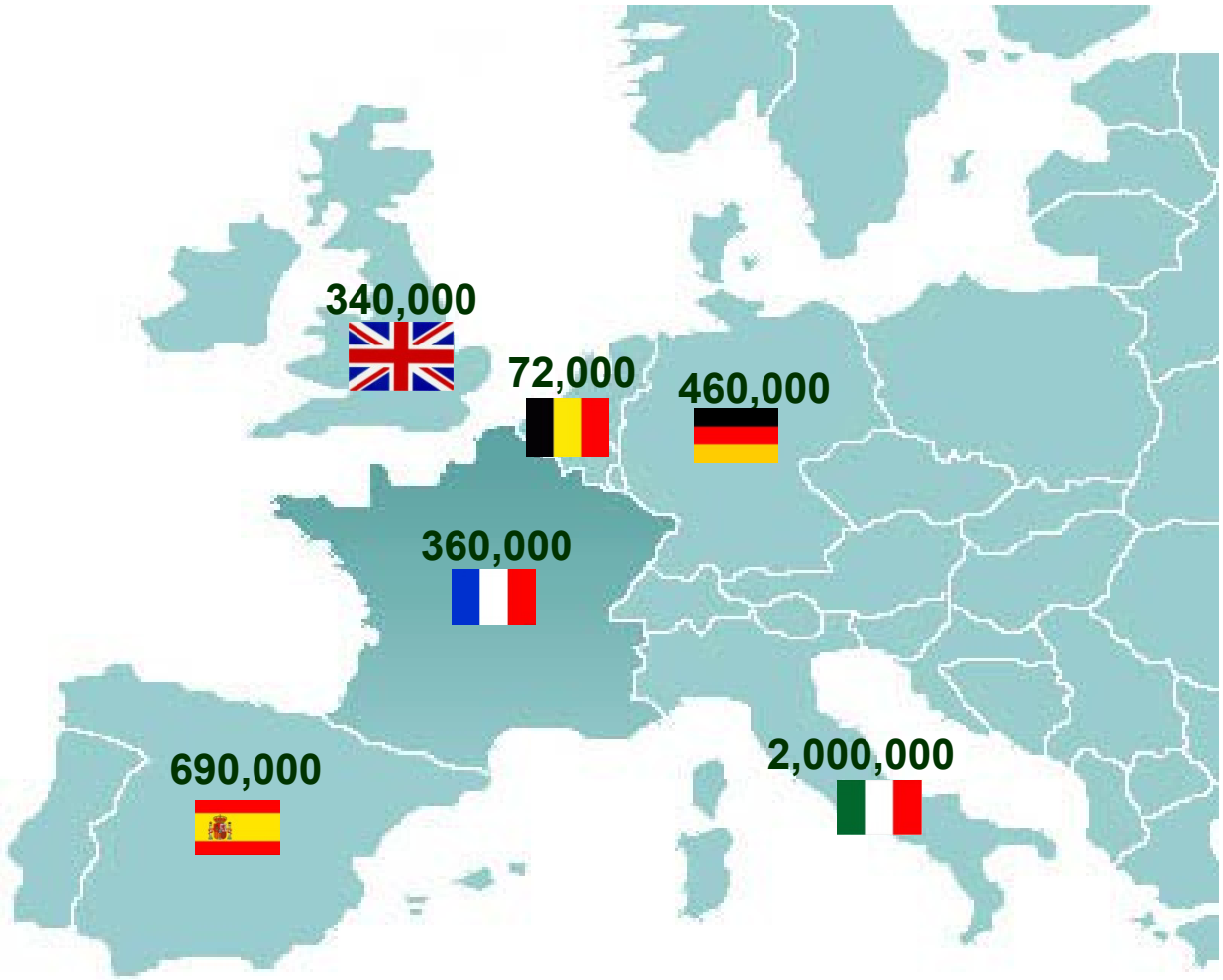
Vierling JM, et al. EASL 2013

Optimize treatment



Select candidates

HCV epidemiology in 2011: Estimation of number of patients ever infected



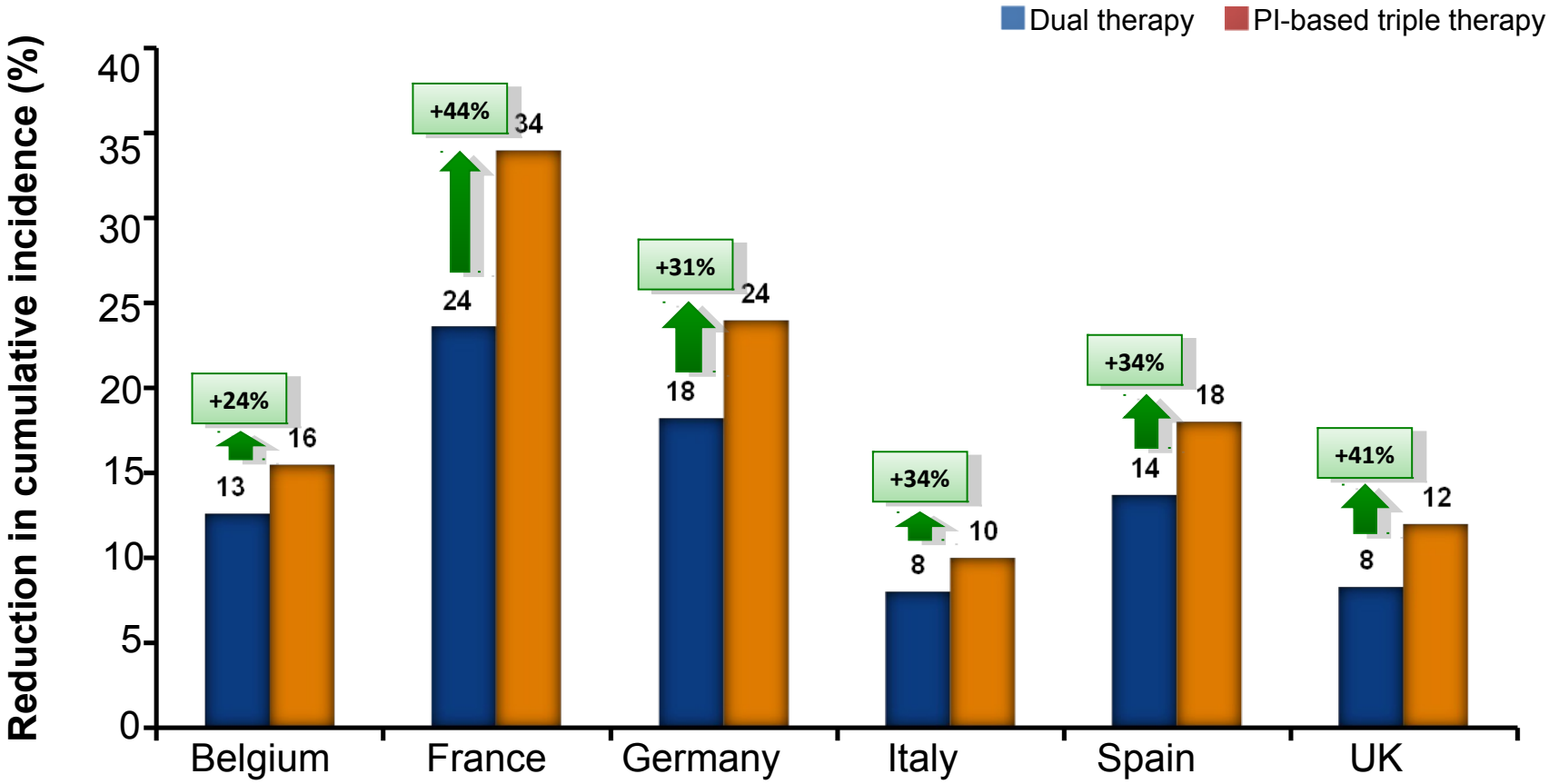
Deuffic-Burban. S et al. Gastroenterology 2012; 143: 974-85.

HCV Screening Rates: 2011 Estimation

	Belgium	France	Germany	Italy	Spain	UK
HCV Screening, %						
Observed, % (yr)	37 (2000)	57 (2004)	40 (2004)	40 (2005)	33 (2008–9)	30 (2004)
Estimated in 2011, %	50	64	48	46	35	34
HCV Genotype						
G1, %	60	56	60	62	65	44
G2/3, %	27	32	37	34	23	53
Other genotypes, %	13	12	3	4	12	3

Deuffic-Burban. S et al. Gastroenterology 2012; 143: 974-85.

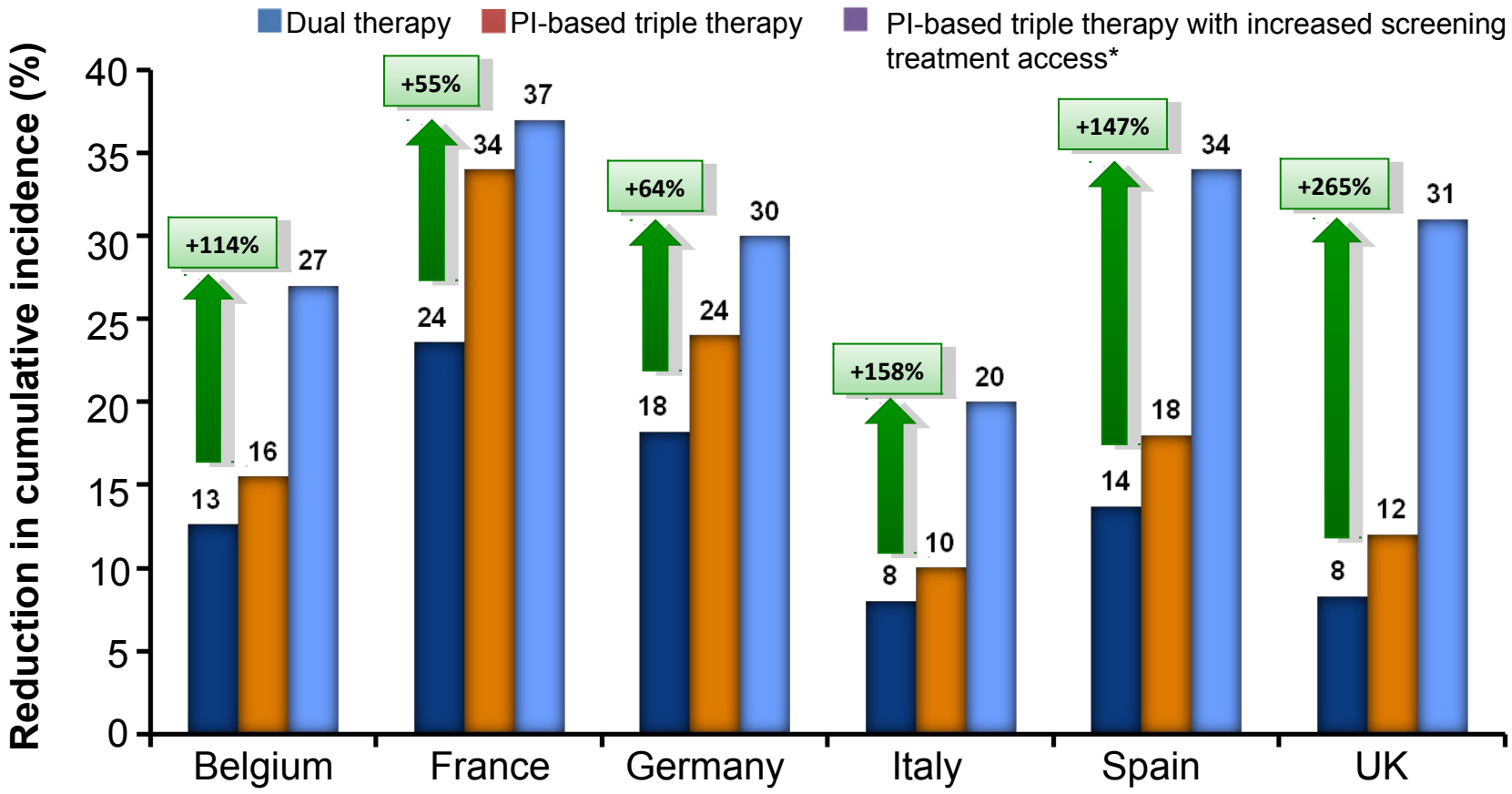
Results: reduction in cumulative incidence of genotype 1 HCV-related cirrhosis, 2012–2021



Greater reduction in HCV-related cirrhosis with PI-based triple therapy than with dual therapy

Deuffic-Burban. S et al. Gastroenterology 2012; 143: 974-85.

Reinforcing screening and treatment access: incidence of genotype 1 HCV-related cirrhosis, 2012–2021

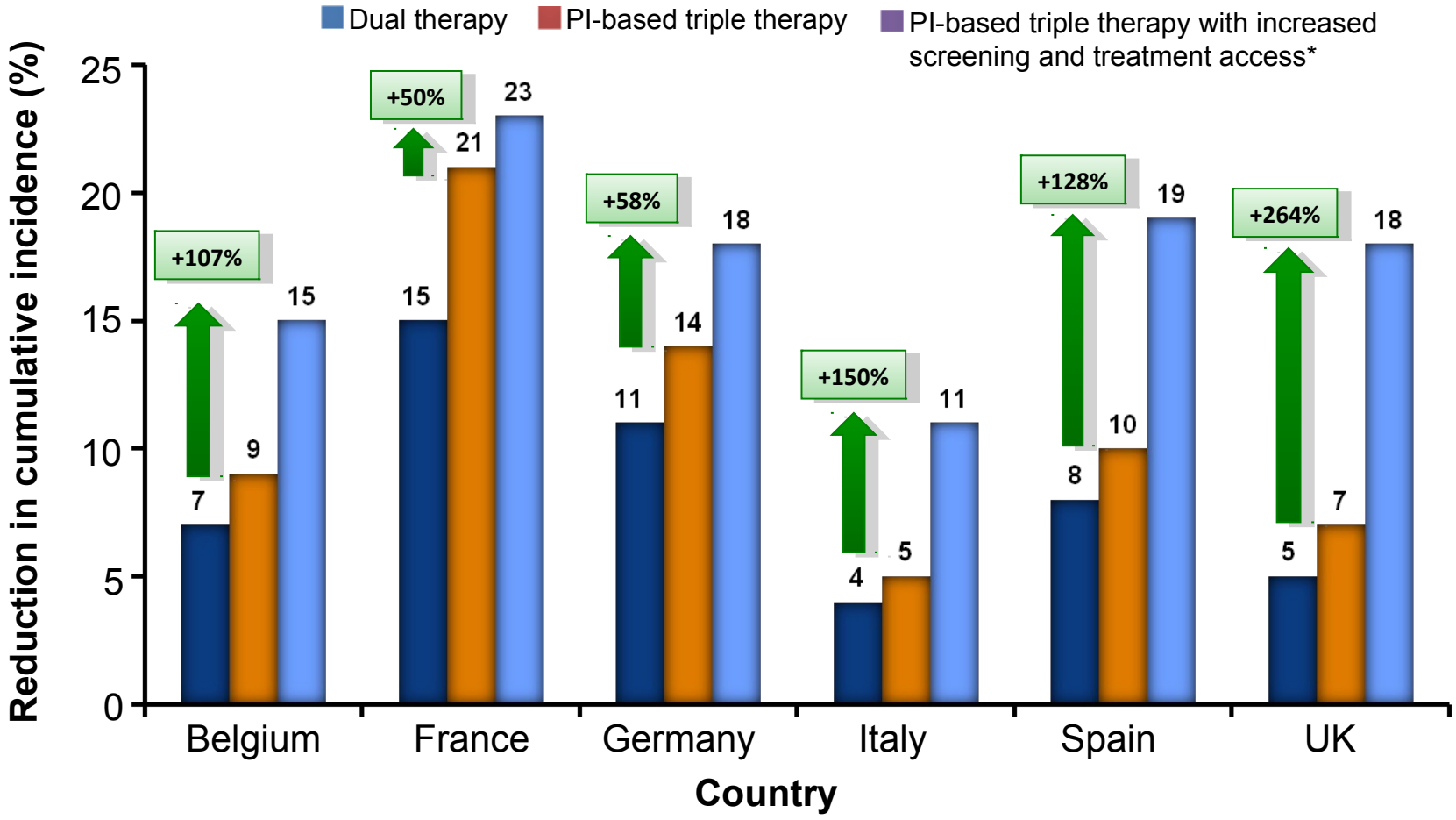


Dramatic reduction in HCV-related cirrhosis with PI-based triple therapy + reinforced screening and treatment access

*Assumes 75% of HCV-infected patients will be screened by 2015 and one G1-infected patient in 2 will be treated in 2015 with PI-based triple therapy

Deuffic-Burban. S et al. Gastroenterology 2012; 143: 974-85.

Reinforcing screening and treatment access: cumulative incidence of genotype 1 HCV-related deaths, 2012–2021



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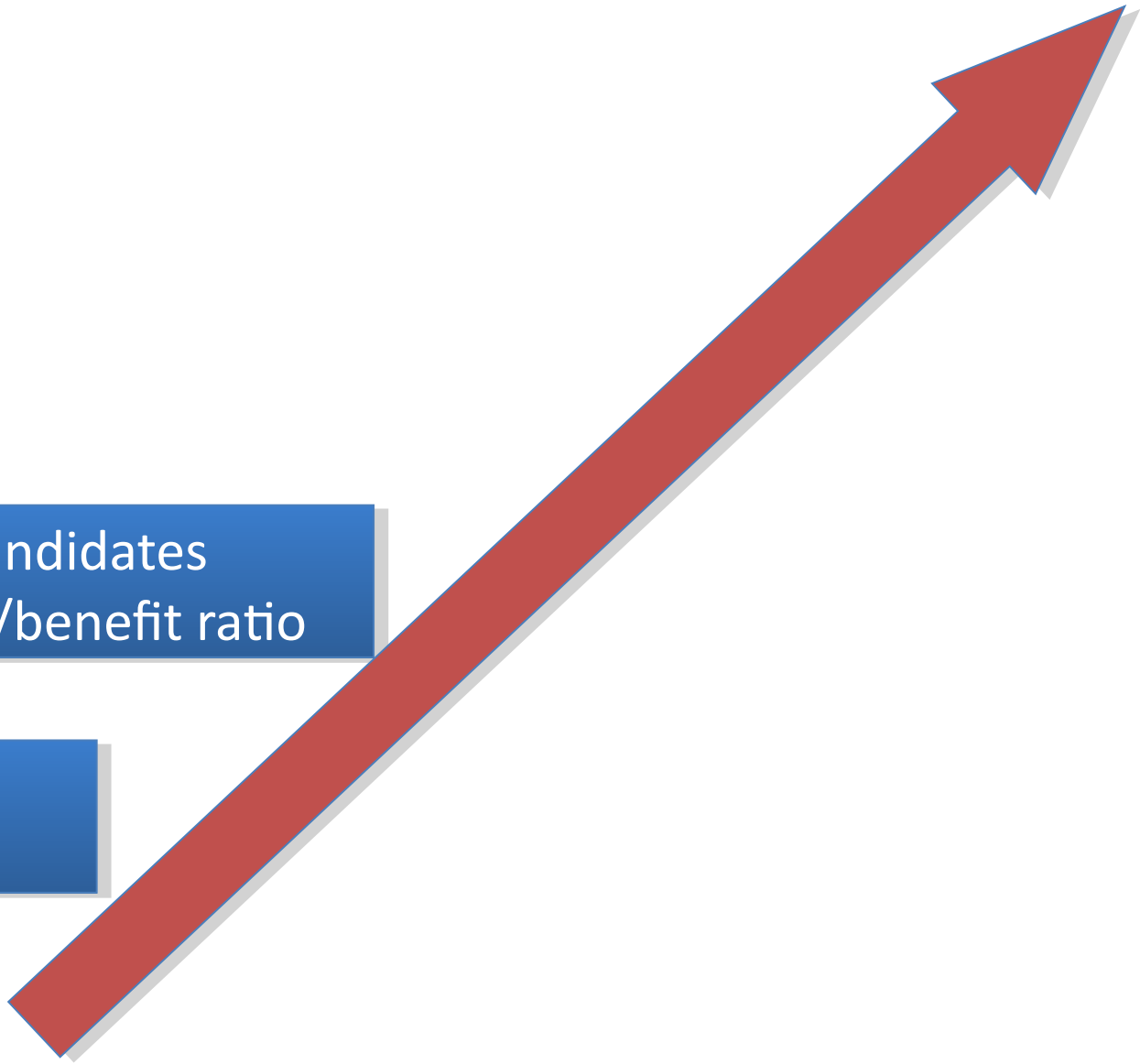
Optimize treatment



Select ideal candidates according to benefit risk ratio

- The good candidates :

Naive

effect	OR (95% CI)	P value
HCV RNA level ≤400,000 vs >400,000	11.6 (1.5-87.8)	.02
IL28B CC vs TT	2.6 (1.3-5.1)	.006
IL28B CC vs CT	2.1(1.2-3.7)	.01
Cirrhosis no vs yes	4.3 (1.6-11.9)	.004
Genotype 1b vs 1a	2.0 (1.2-3.4)	.005
Non Black vs Black	2.0 (1.1-3.7)	.03

Treatment–experienced

effect	OR (95% CI)	P value
Relapser vs non responder	2.6 (1.3-5)	.006

Baseline HCV RNA Level	SVR (%)
≤ 1,000,000 IU/ml	78% - 83%
> 1,000,000 IU/ml	57% -68%

Gordon SC et al. J Clin Gastroenterol 2013.

Poordad F et al. Gastroenterology 2012; 143: 608-618..

Select ideal candidates according to benefit risk ratio

- The patient who do not be trea

Risk factors for SAE	Platelets count > 100,000/mm³	Platelets count ≤ 100,000/mm³
Albumin 35 g/L	SVR >> SAE (306)	SVR > SAE (74)
Albumin <35 g/L	SAE: 16.1 % SVR > SAE	SAE: 51.4 % SAE >> SVR

Missing data in 69 patients

9%

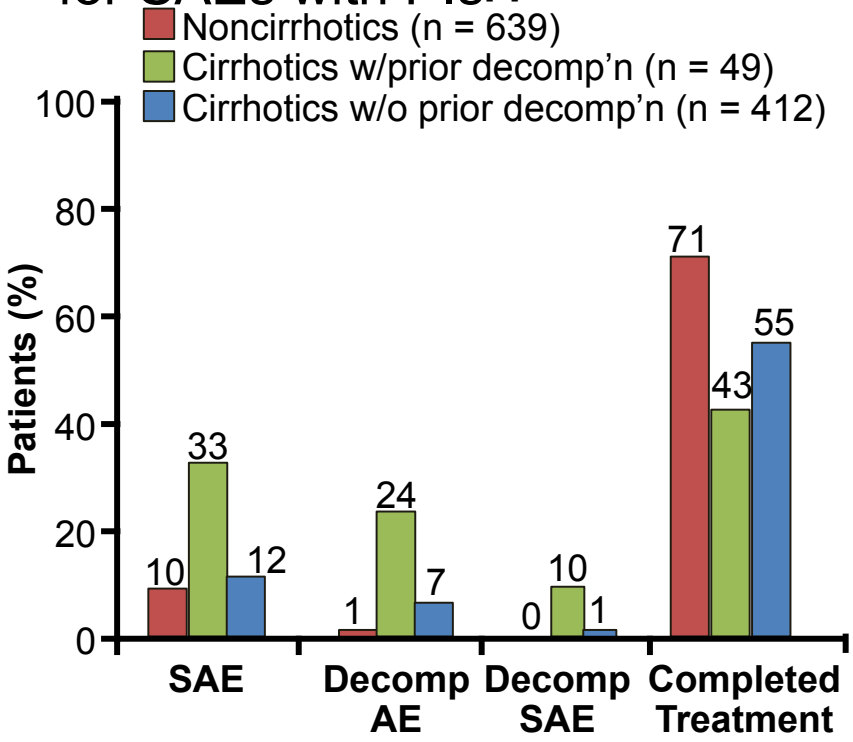
Fontaine H et al . AFEF 2013

HCV-TARGET: Risk Factors for Poor Outcomes in PI-Treated Pts

- Risk factors for decompensation among cirrhotic patients during PI therapy identified[1]

Baseline Characteristic	Odds Ratio Minimally Adjusted Estimates	*P* Value
CrCl (mL/min)	0.99	.03
Albumin (g/dL)	0.30	< .01
HCV RNA (log IU/mL)	0.76	< .01
Bilirubin (log mg/dL)	2.93	.02

- Pts with history of decompensation at highest risk for SAEs with PIs[2]

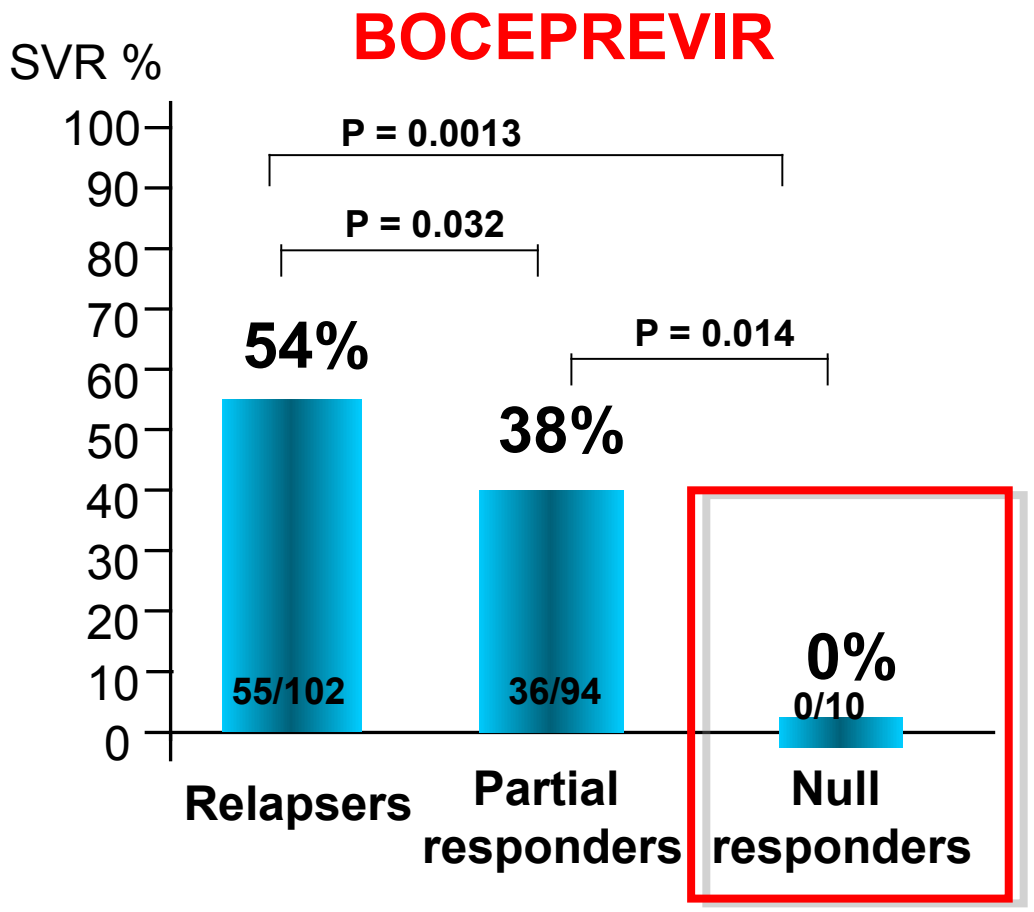


1. Afdhal N, et al. AASLD 2013. Abstract 1865.

2. Gordon S, et al. AASLD 2013. Abstract 1866.

Select ideal candidates according to benefit risk ratio

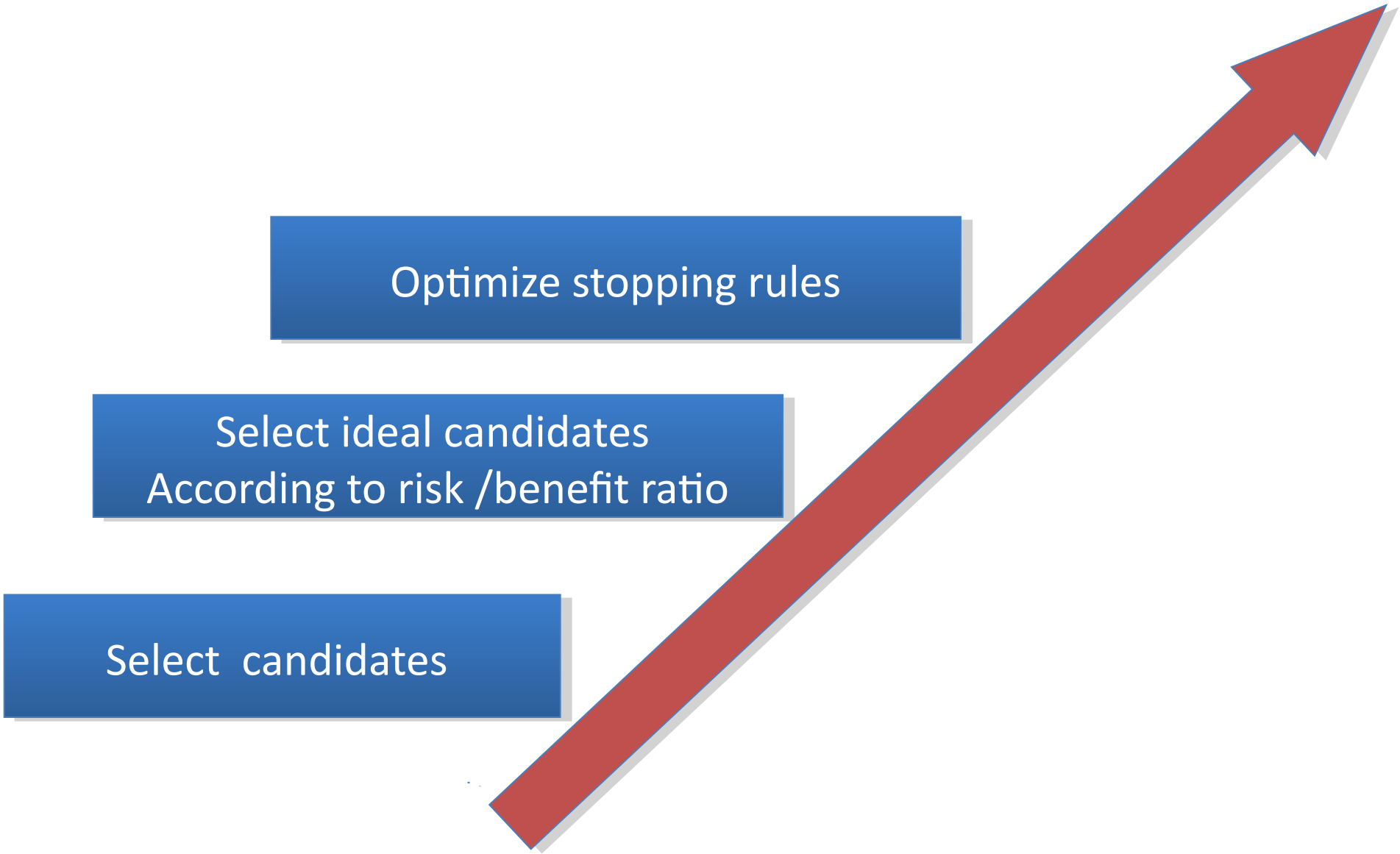
- The patient who do not be treated : Null responder cirrhotic



CUPIC AnrS CO20

Fontaine H , France, AFEF 2013,

Optimize treatment



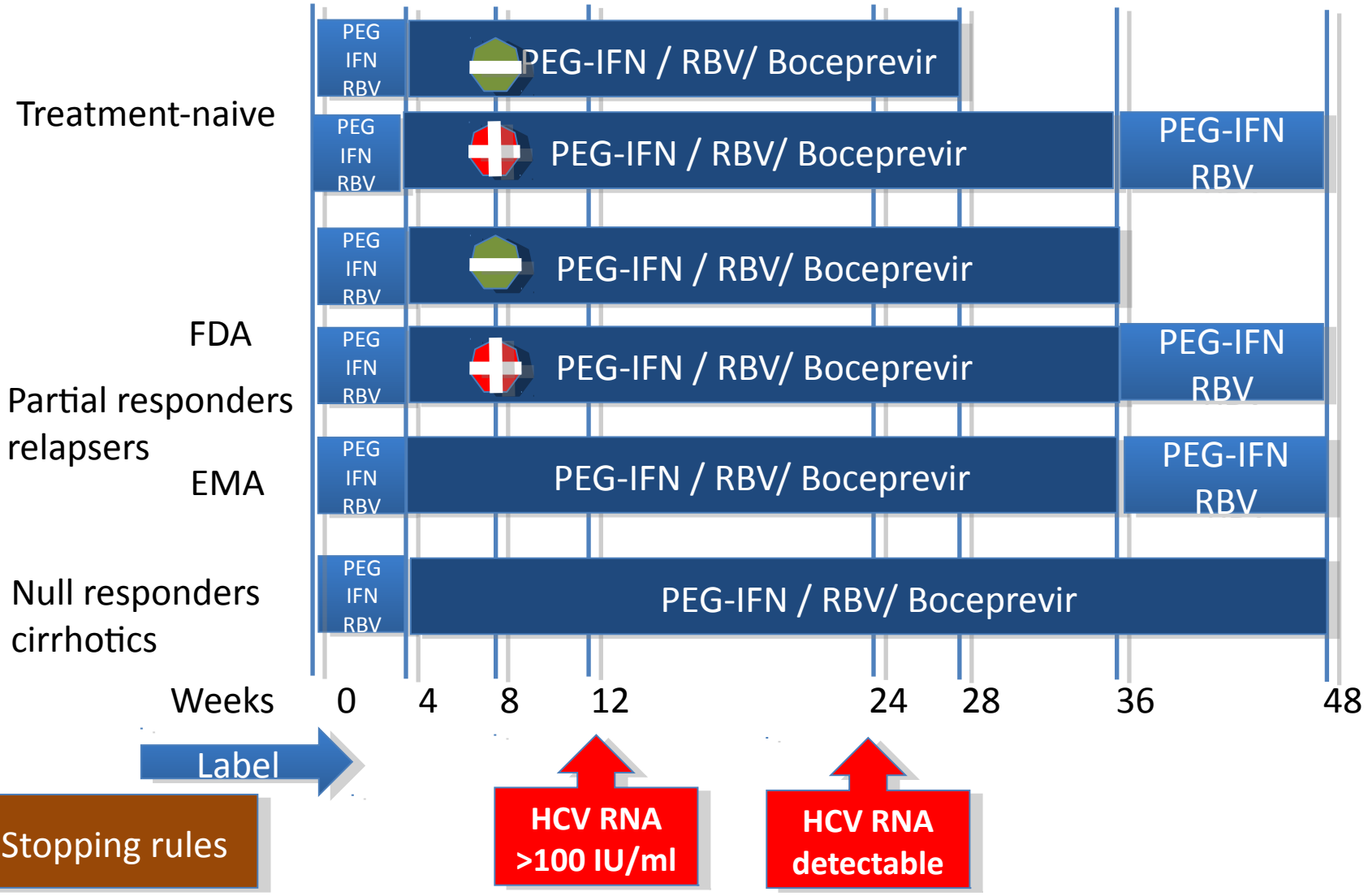
Optimize stopping rules

Naive patients

Threshold HCV RNA Level	Week 8 Stopping Rule (n = 672)*				Week 12 Stopping Rule (n = 670)†			
	Patients Stopped by Week 8 Rule (n)	Additional Patients Stopped by Week 24 Rule (n)	Total Patients Stopped (n)	SVR Missed With Week 8 Rule (n)	Patients Stopped by Week 12 Rule (n)	Additional Patients Stopped by Week 24 Rule (n)	Total Patients Stopped (n)	SVR Missed With Week 12 Rule (n)
≥9.3 IU/mL (LLD)	260	11	271	98	144	20	164	21
≥25 IU/mL (LLQ)	155	25	180	31	83	41	124	5
≥50 IU/mL	147	26	173	26	78	43	121	4
≥100 IU/mL	120	32	152	16	65	49	114	0
≥1000 IU/mL	61	57	118	4	43	61	104	0
<2-log decline from the baseline	13	74	87	0	24	71	95	0
<3-log decline from the baseline	34	66	100	1	34	66	100	0

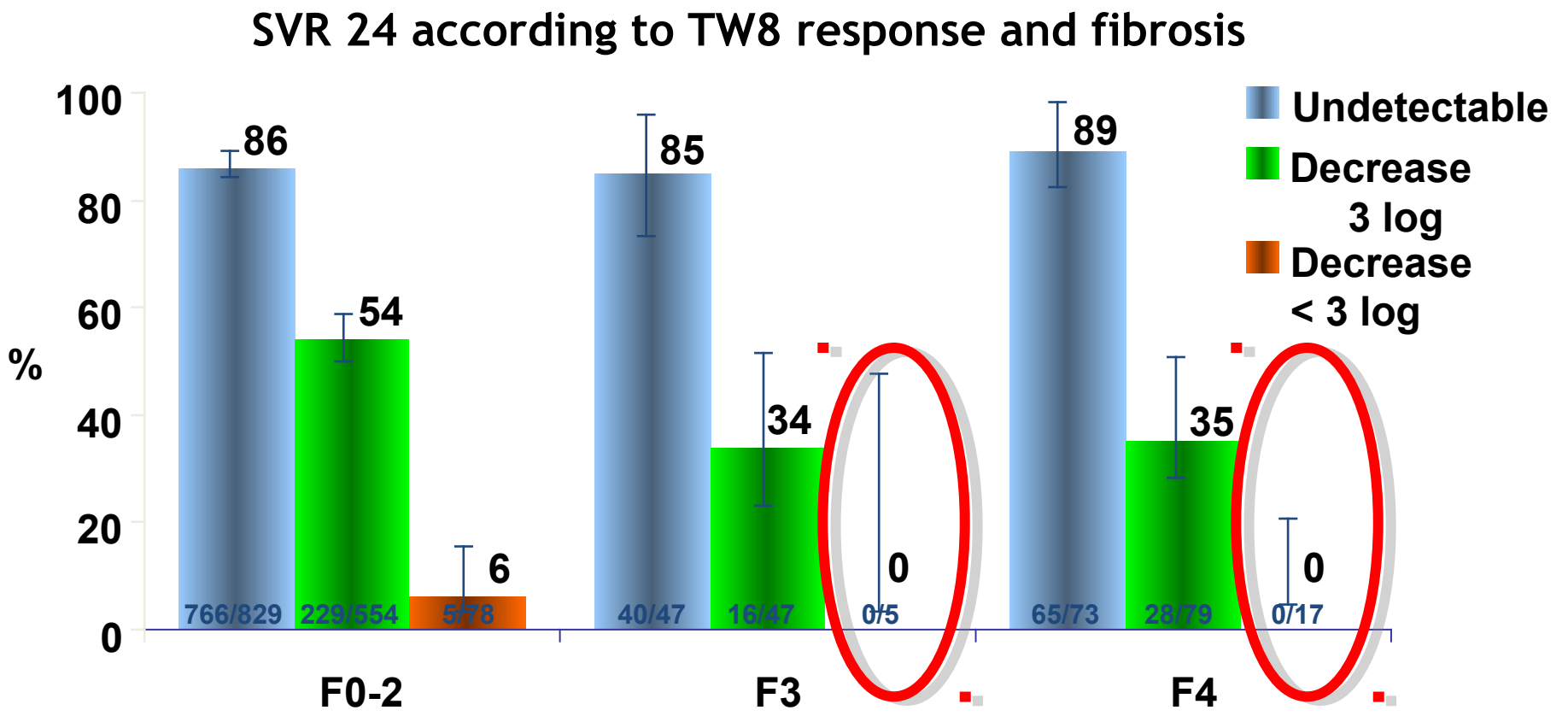
Jacobson I et al. Hepatology 2012; 56: 567-575.

Optimize stopping rules



Optimize stopping rules

- **Boceprevir : New TW8 stopping rules in patients with advance fibrosis or cirrhosis**

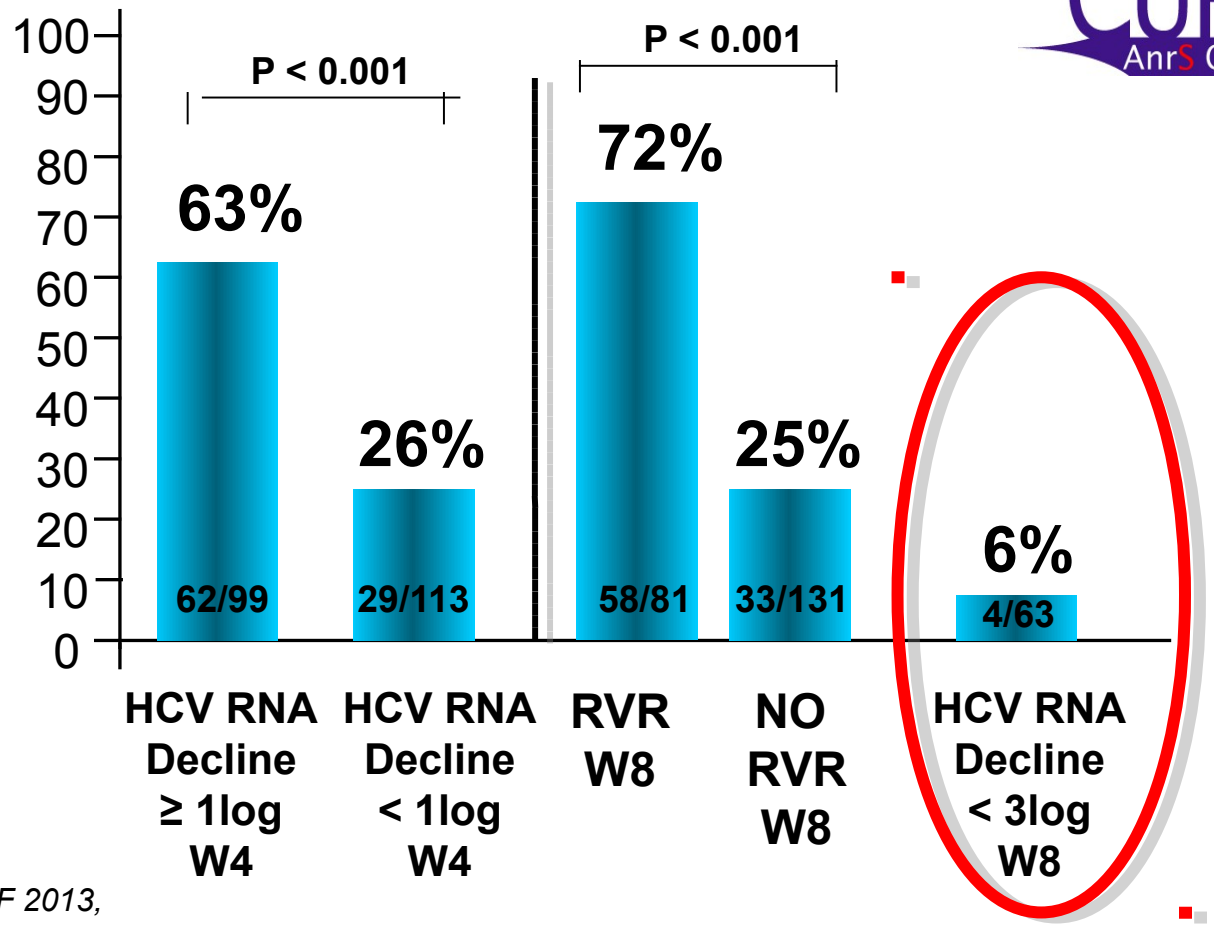


➔ Early viral kinetics allows to stop or continue treatment.

Vierling JM et al. EASL 2013, Abs. 1430

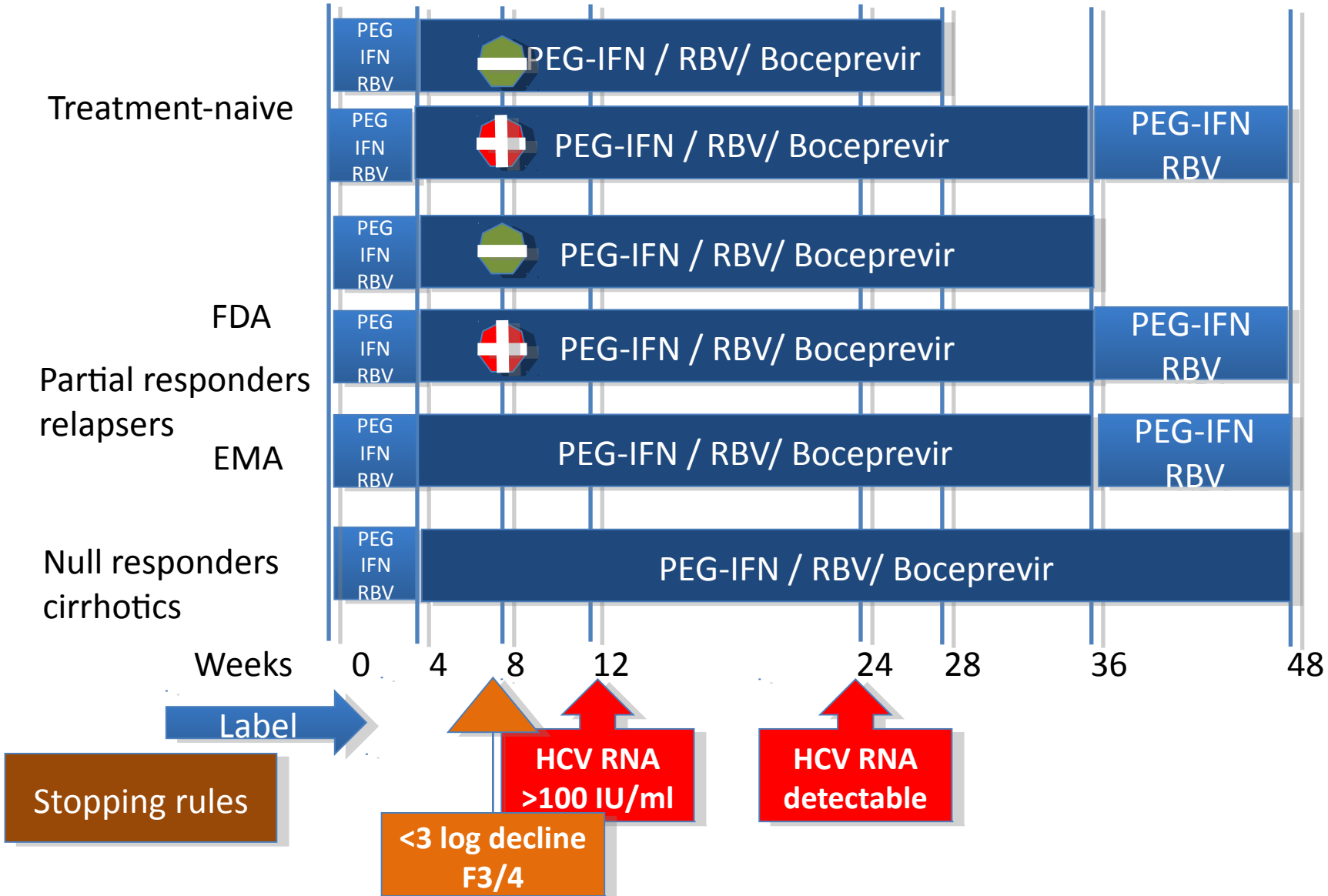
Optimize stopping rules

- **Boceprevir : New TW8 stopping rules in patients with cirrhosis**

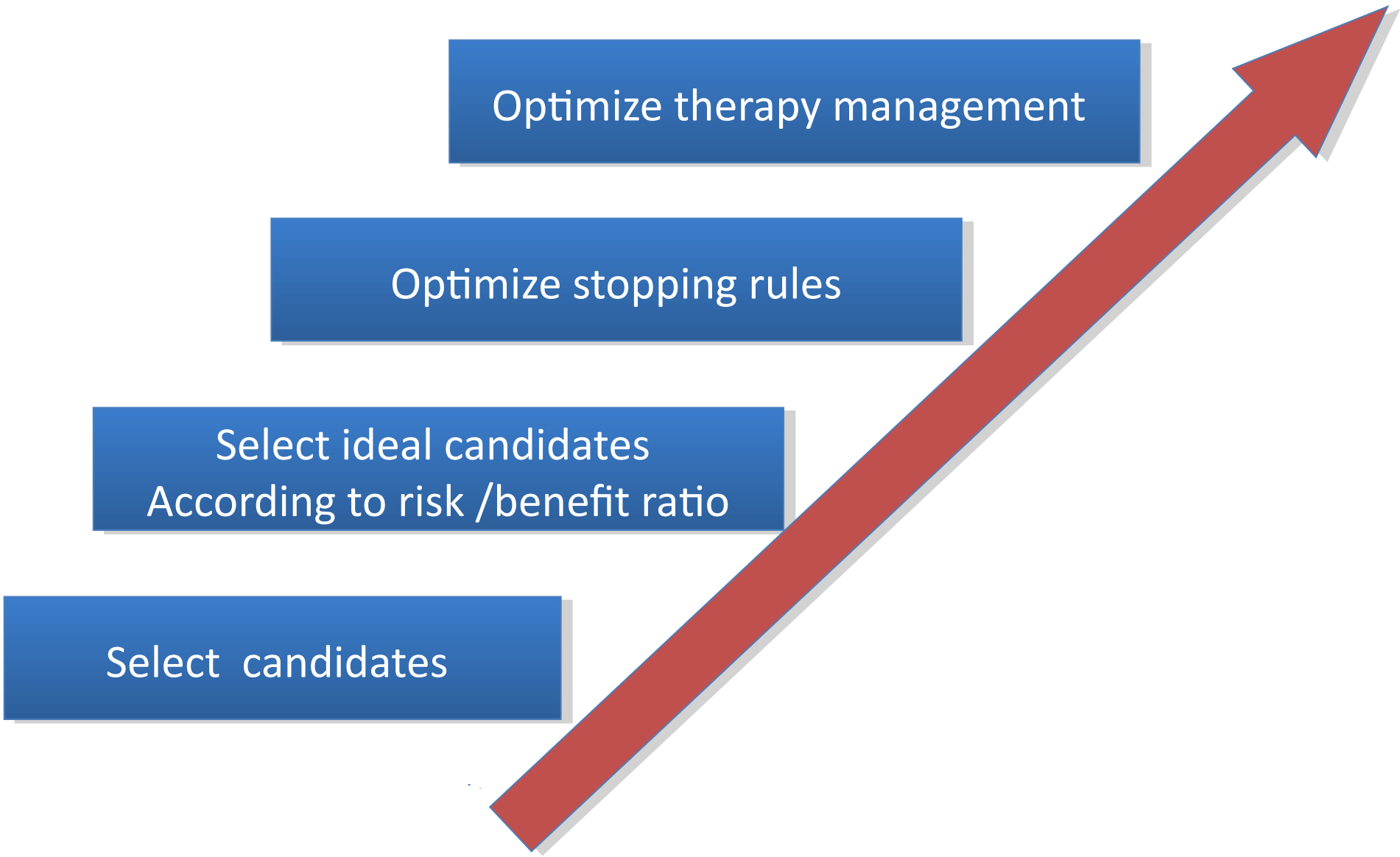


Fontaine H , France, AFEF 2013,

Optimize stopping rules



Optimize treatment



Side effects

Telaprevir

Rash (55%) vs 33%

Severe 5%

Anemia x2 (32% vs 15%)

Anorectal symptoms(26% vs6%)

McHutchison J et al, N Engl J Med 2009; 360 : 1827-1838.
Hezode C et al . N Engl J Med 2009; 360: 1839-1850.
Jacobson IM et al. N Engl J Med 2011; 364: 2405-16.
Zeuzem S, et al. N Engl J Med 2011;364:2417–28.

Boceprevir

Anemia x 2 (≈50% vs 25%)

Dysgeusia (37-45% vs 11-18%)

Neutropenia $< 750/mm^3$ 20-24% vs 9-14%

Kwo P et al. Lancet 2010; 376: 705-716.
Poordad F. N Engl J Med. 2011; 364:1195-1206.
Bacon BR., et al. N Engl J Med 2011; 364:1207-1217..
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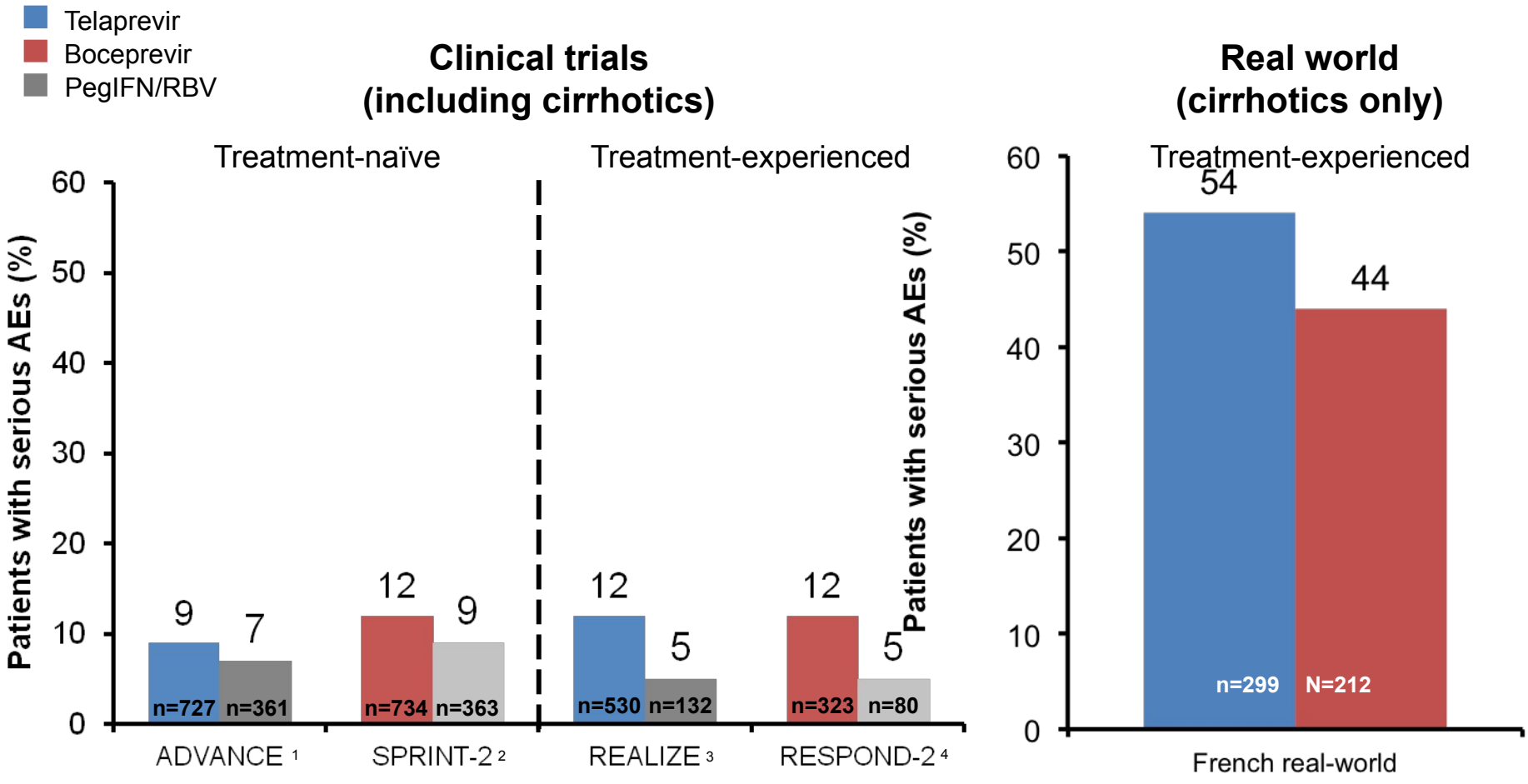
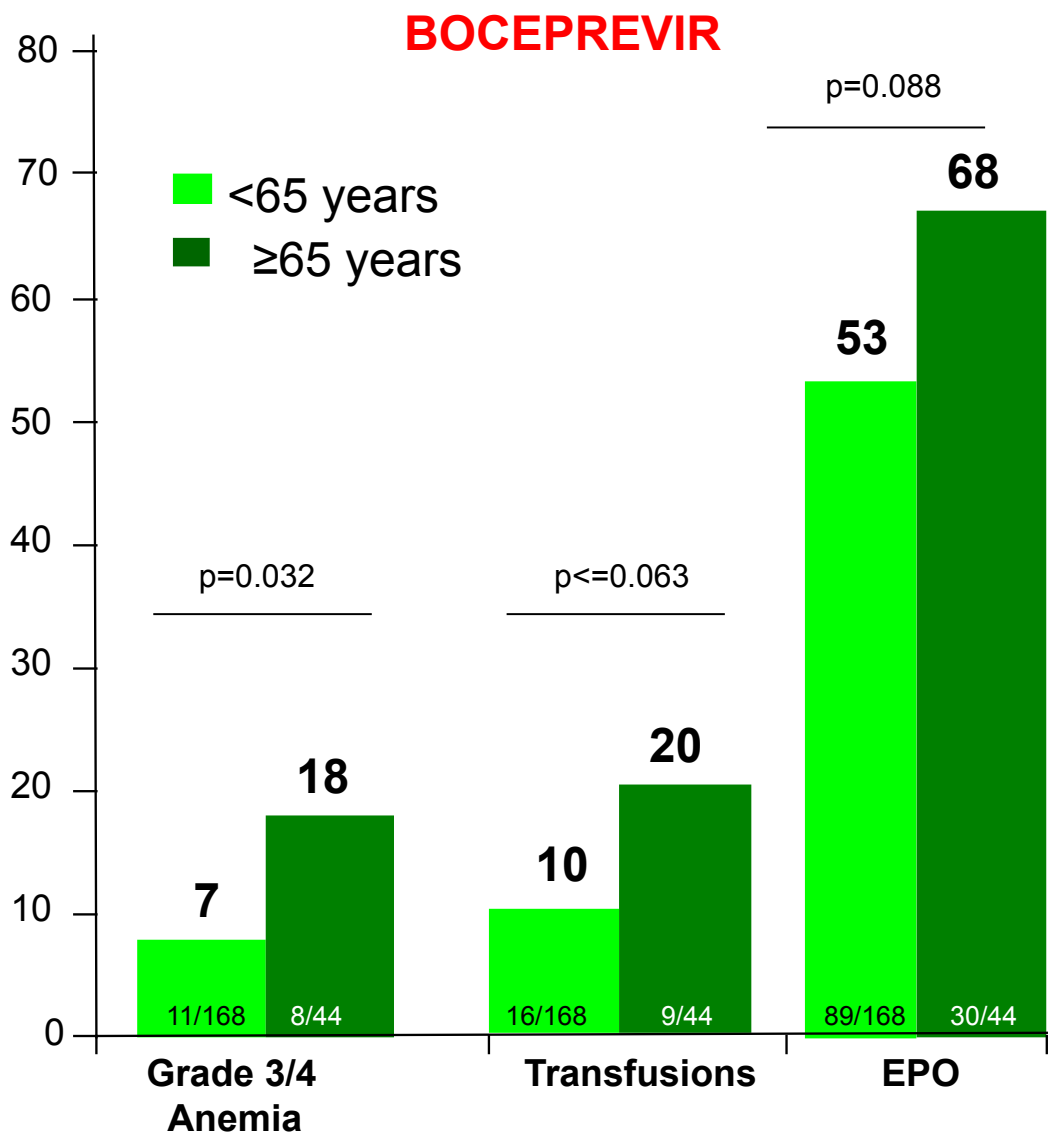
Clinical Trials *vs* Real World

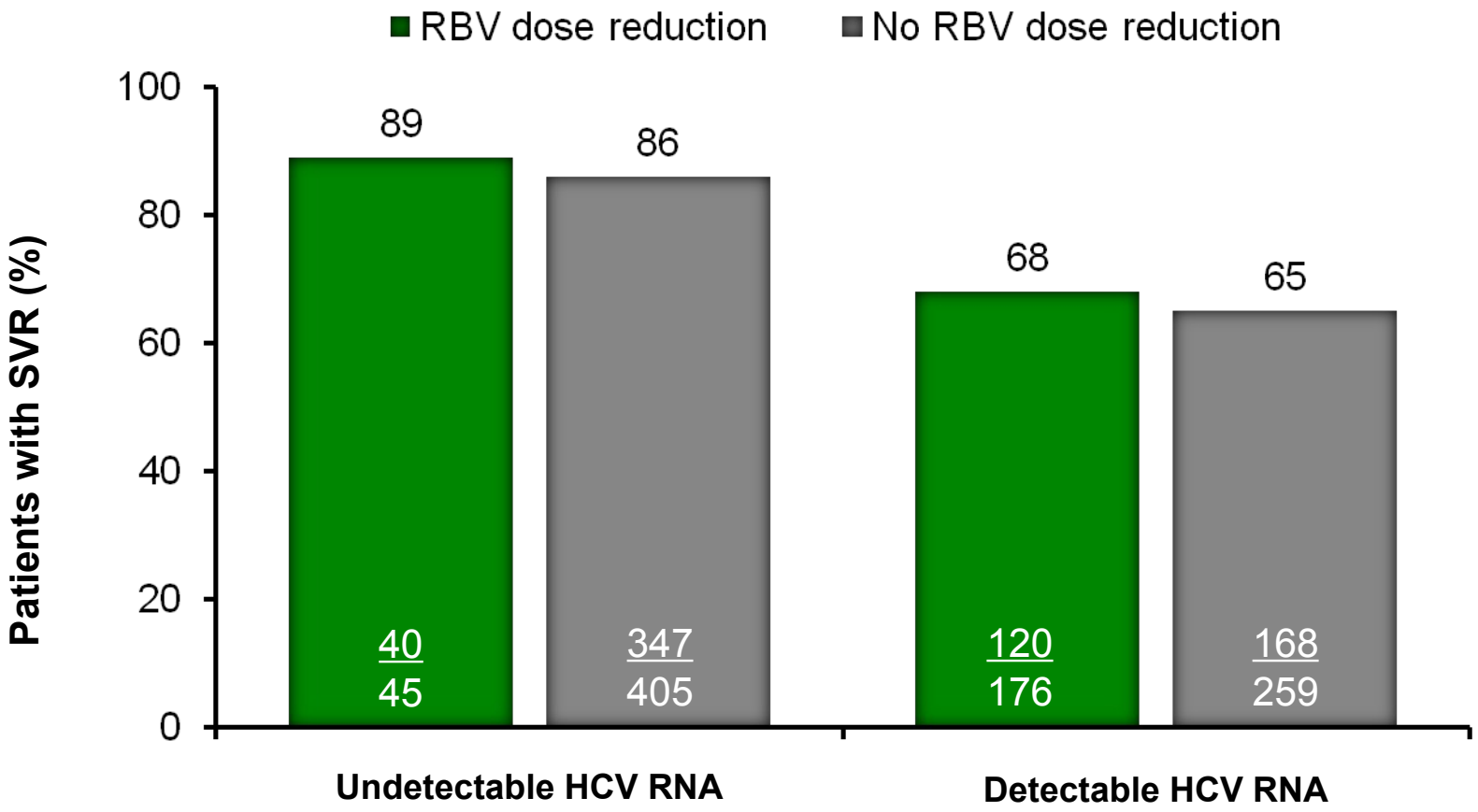


Anemia management according to age



Hézode C, et al. AASLD 2013

SVR according to time of first RBV dose reduction during first 4 weeks of treatment and HCV RNA status

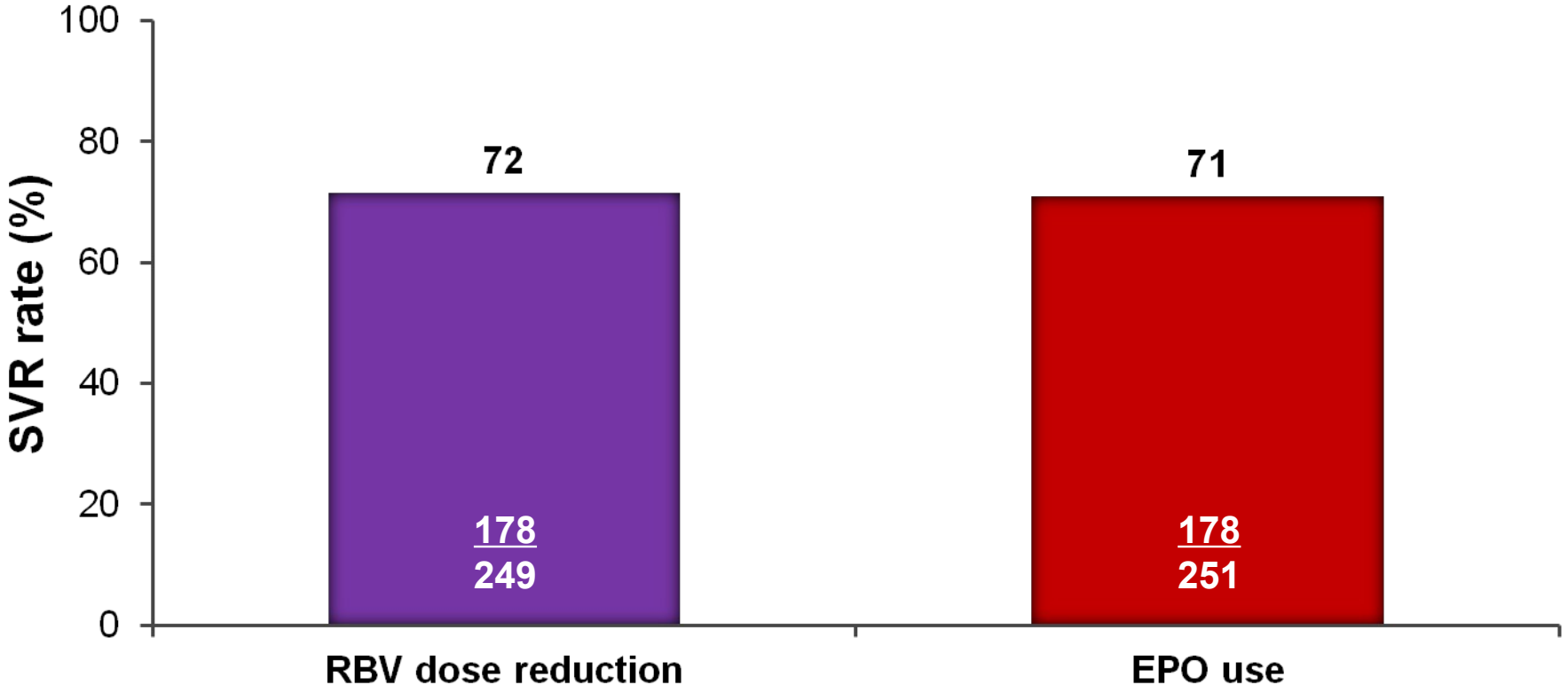


- **Small sample sizes among previously treated patients limit interpretation of data in REALIZE, however similar trends were observed**

Treatment-naïve patients in ADVANCE/ILLUMINATE (N=885)

Sulkowski MS, et al. J Hepatol 2012;56(Suppl. 2):S459–60

Boceprevir: similar SVR when RBV dose modification and EPO are used to manage anemia

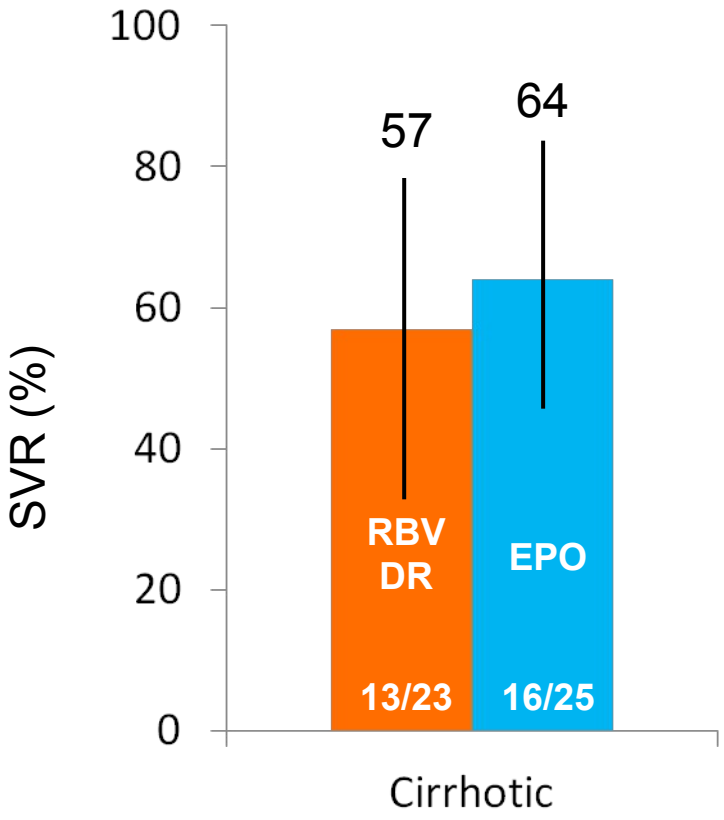


Treatment-naïve G1 patients (n=687) received BOC-based therapy. Overall, 500 patients developed anemia (Hb ≤10 g/dL or were expected to reach that nadir before next visit) and were randomized to have anemia managed with either EPO (40 000 units/week SC), or RBV dose reduction (by 200–400 mg/day). Transfusion in patients with Hb ≤8.5 g/dL was allowed to prevent study discontinuation

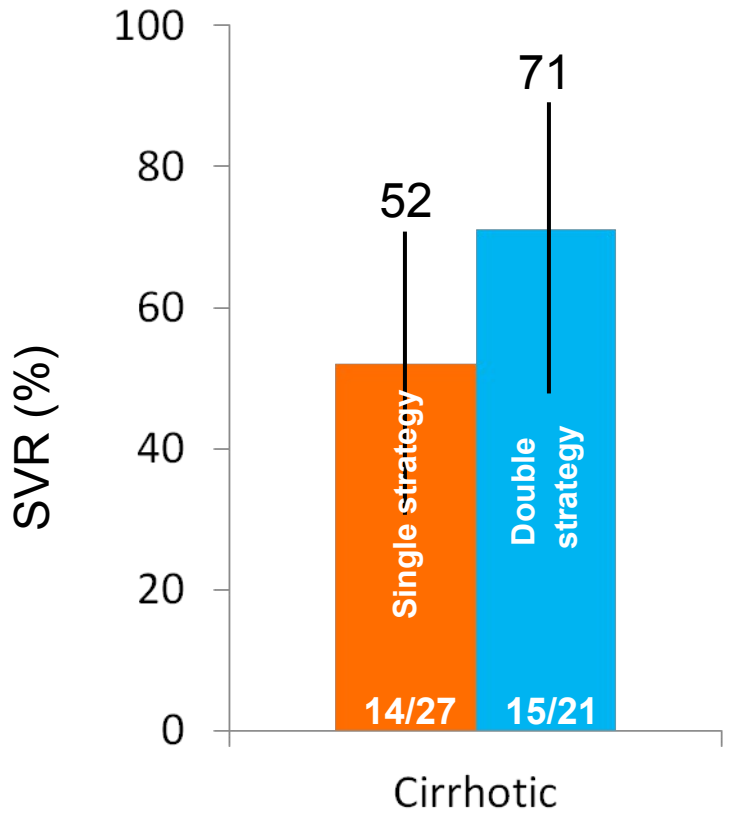
Poordad F, et al. EASL 2012. Abstract 1419

Genotype 1 cirrhosis and boceprevir : RBV dose reduction or EPO use ?

SVR according to RBV DR or EPO use



SVR according to the need of single or double strategy



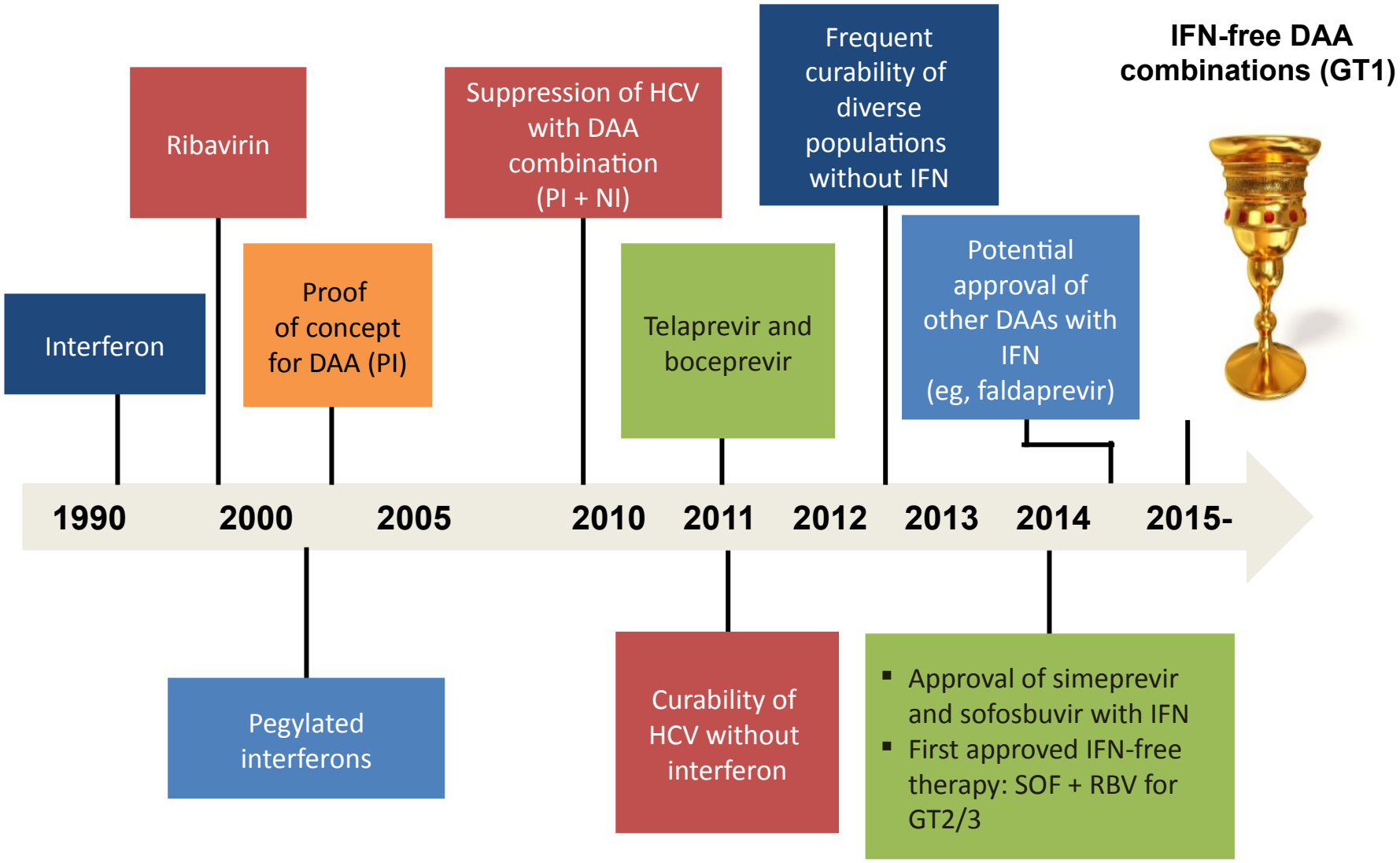
RBV DR : RBV dose reduction

Lawitz E, Etats-Unis, AASLD 2012, Abs. 50 actualisé

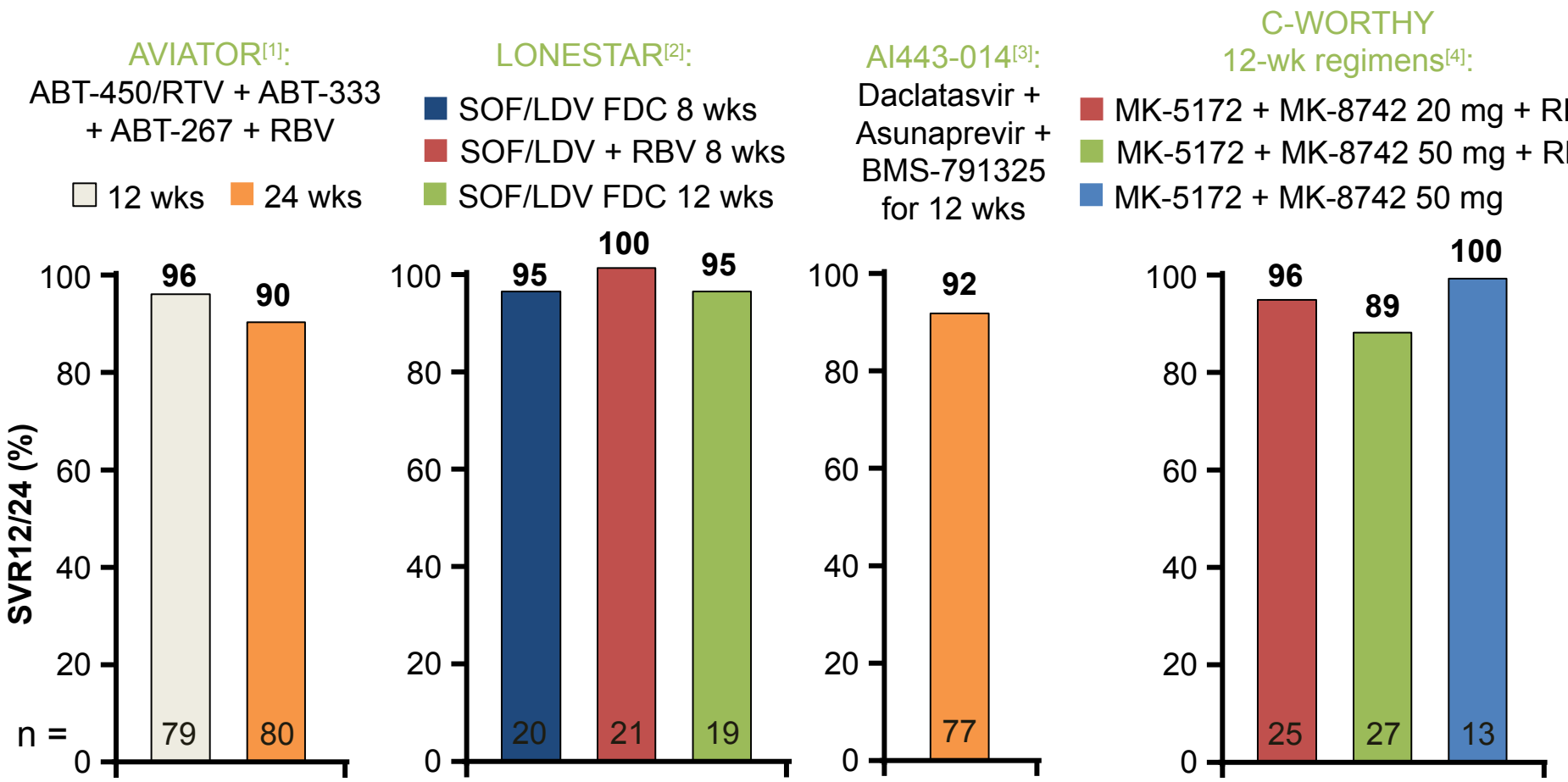
Conclusions

- Triple therapies with Pis are a major advance in the history of HCV treatment.
- Optimal patients selection is crucial to achieve high SVR rate with reasonable safety profile
- Optimizing BOC treatment includes:
  - Optimizing treatment design according to baseline characteristics
  - Following optimal stopping rules
  - Preventing DDIs
  - Preventing and managing AEs

HCV Therapy: Past, Present and Future



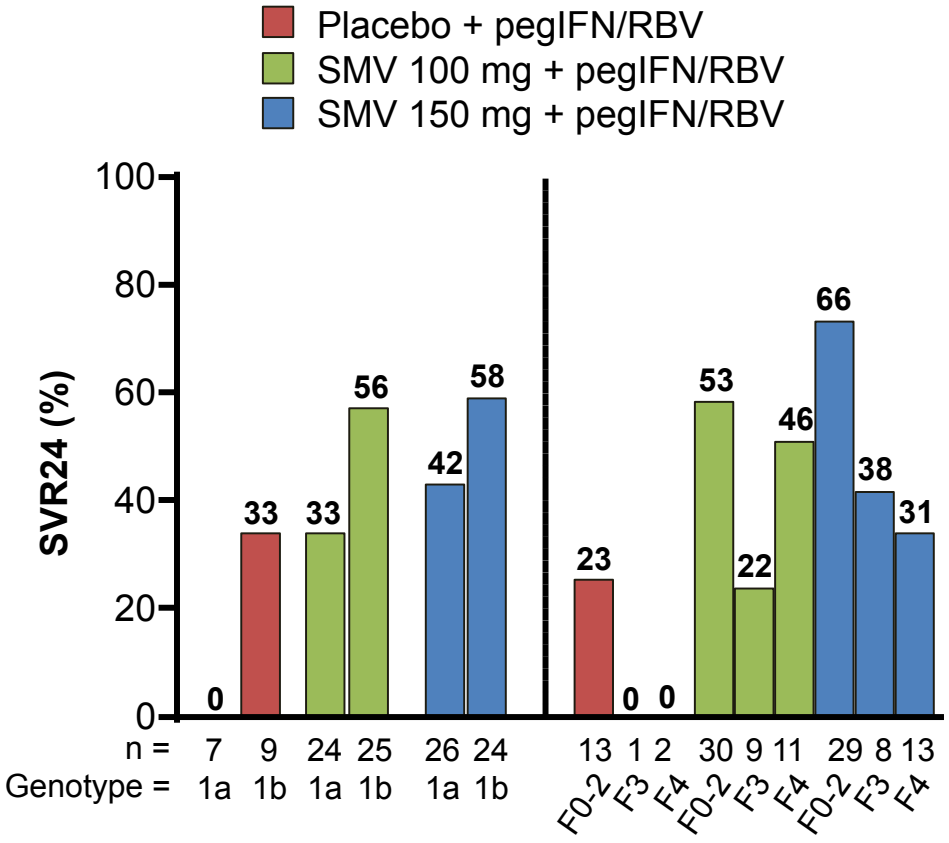
IFN-Free Therapy for Tx-Naive GT1 HCV: Regimens Effective in Both Subtypes



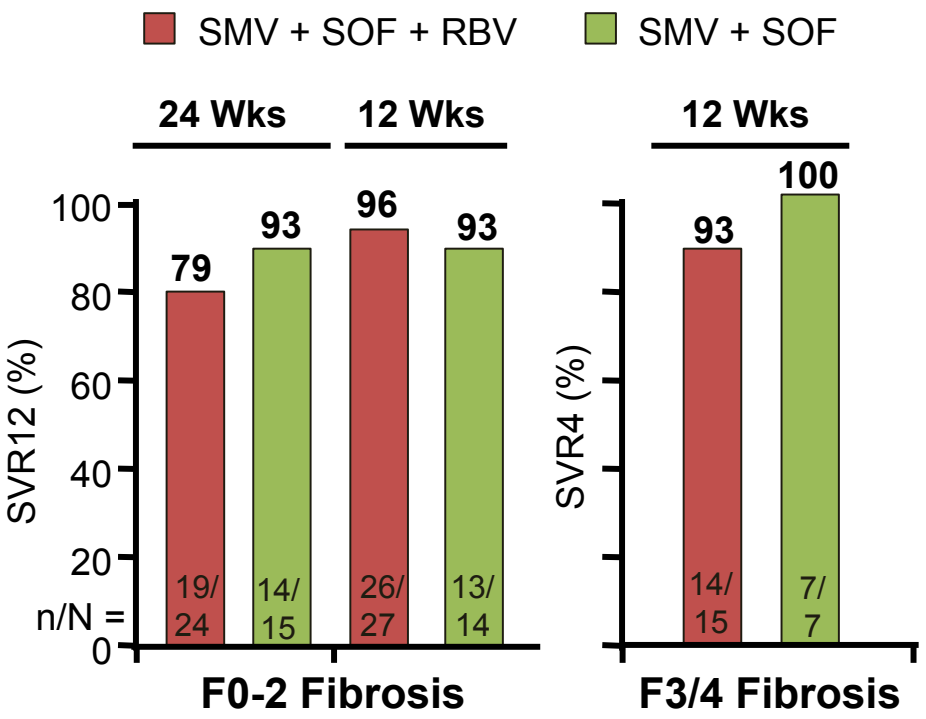
1. Kowdley K, et al. EASL 2013. Abstract 3. 2. Lawitz E, et al. AASLD 2013. Abstract 215.
3. Everson GT, et al. AASLD 2013. Abstract LB-1. 4. Lawitz E, et al. AASLD 2013. Abstract 76.

Efficacy of Simeprevir and/or Sofosbuvir in Previous Null Responders

Phase IIb Trial of Simeprevir + PegIFN/RBV[1]



COSMOS[2]



1. Zeuzem S, et al. Gastroenterology 2013;[Epub ahead of print].

2. Jacobson IM, et al. AASLD 2013. Abstract LB-3.