

Hepatitis C

Diagnose, Therapie und Verlaufskontrolle

Molekulare Diagnostik 2010
Weiter- und Fortbildungs-Symposium
3.-4. März 2010

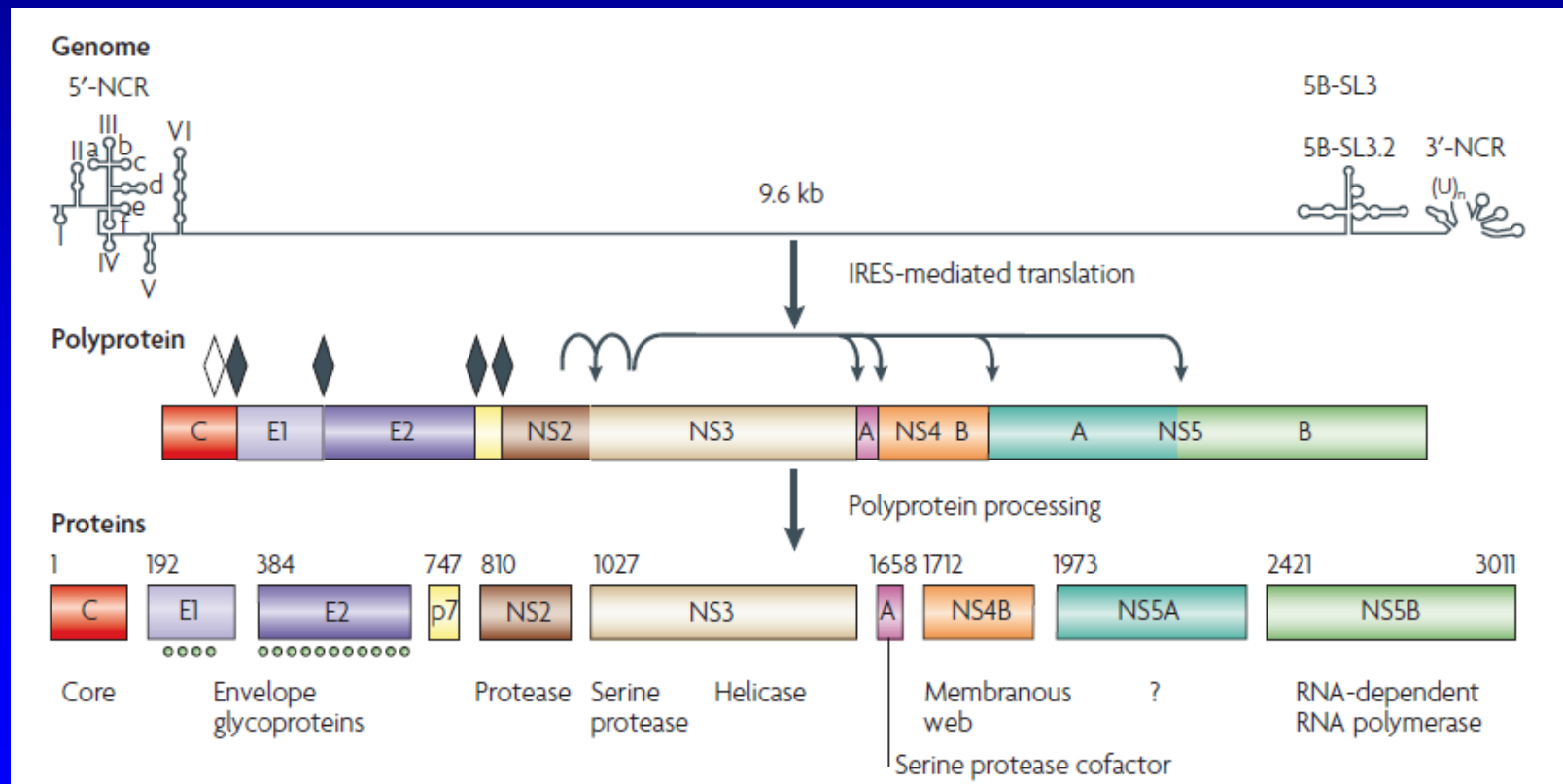
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University Hospital Zurich

Hepatitis C

- **Epidemiology**
- **Natural history**
- **Diagnosis**
- **Therapy**

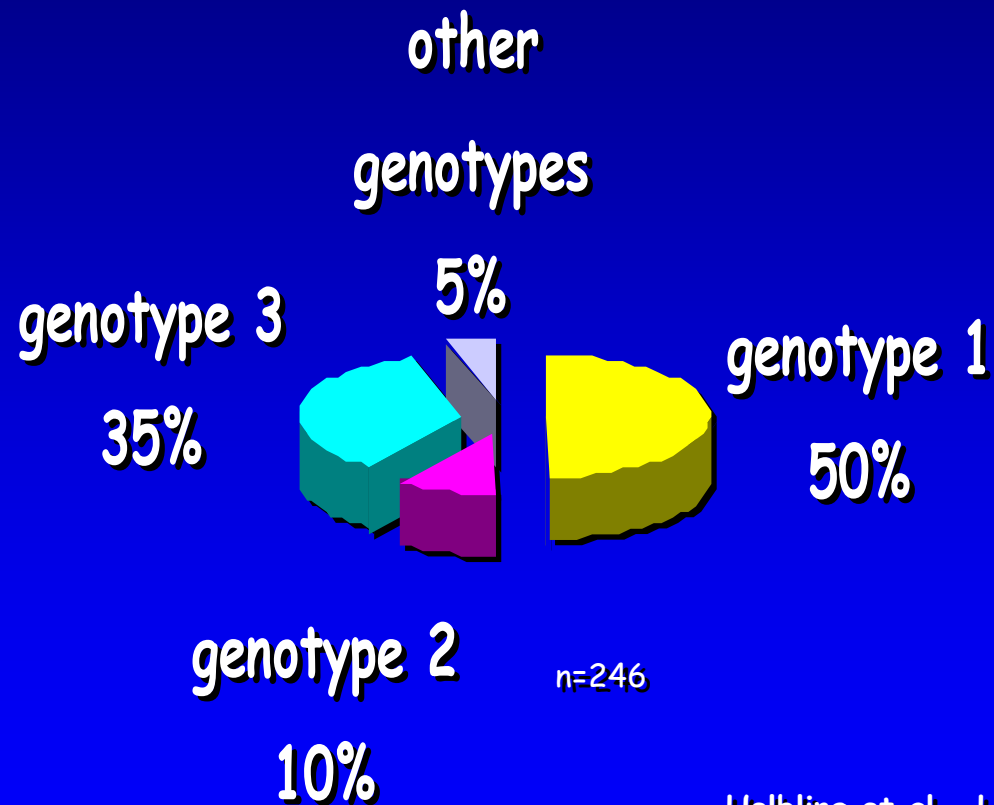
Hepatitis C Virus

- Small RNA-Virus
- Flaviviridae Family
- 6 Genotypes



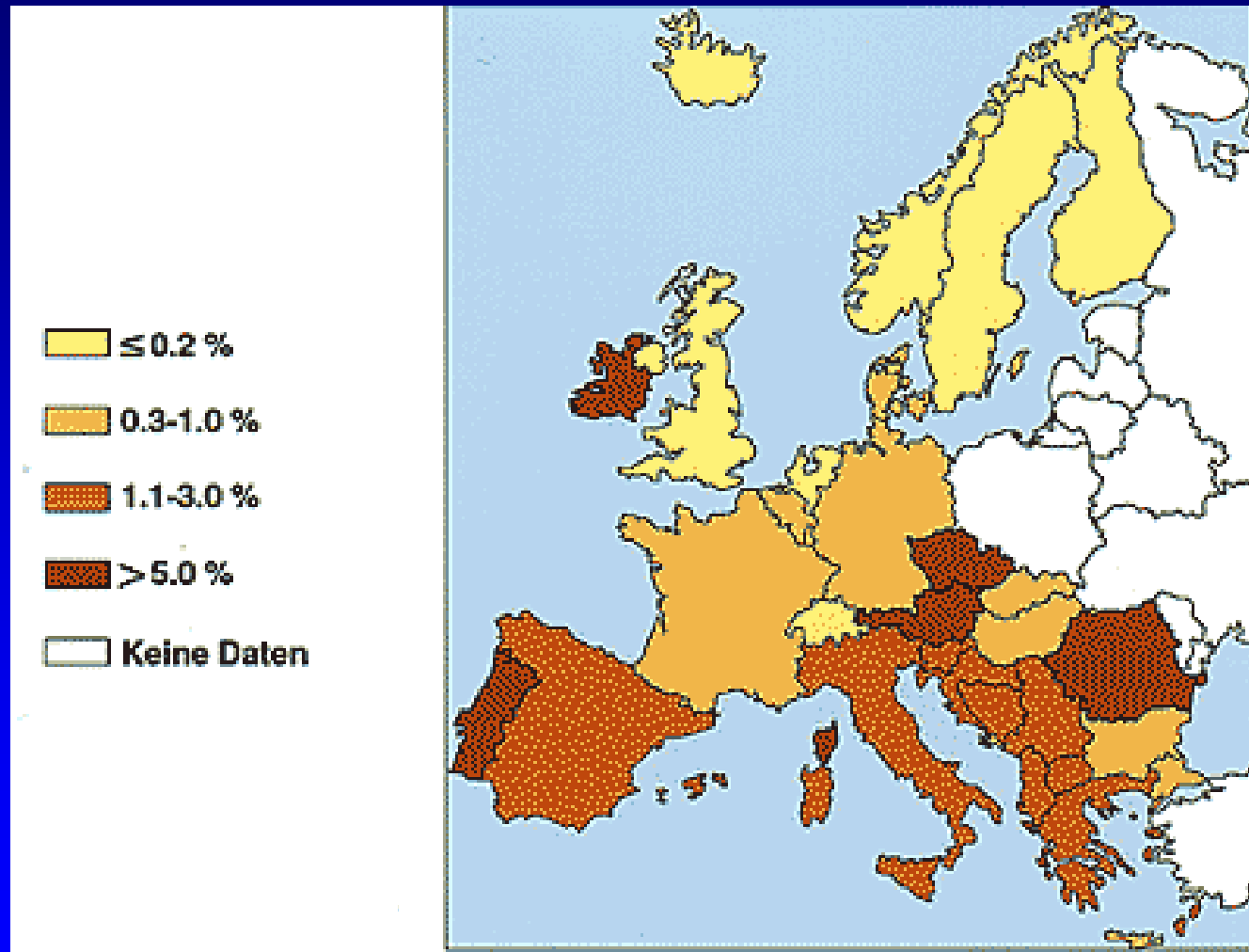
Moradpour et al., Nature Review Microbiol 2007;5:453-63

Hepatitis C Virus



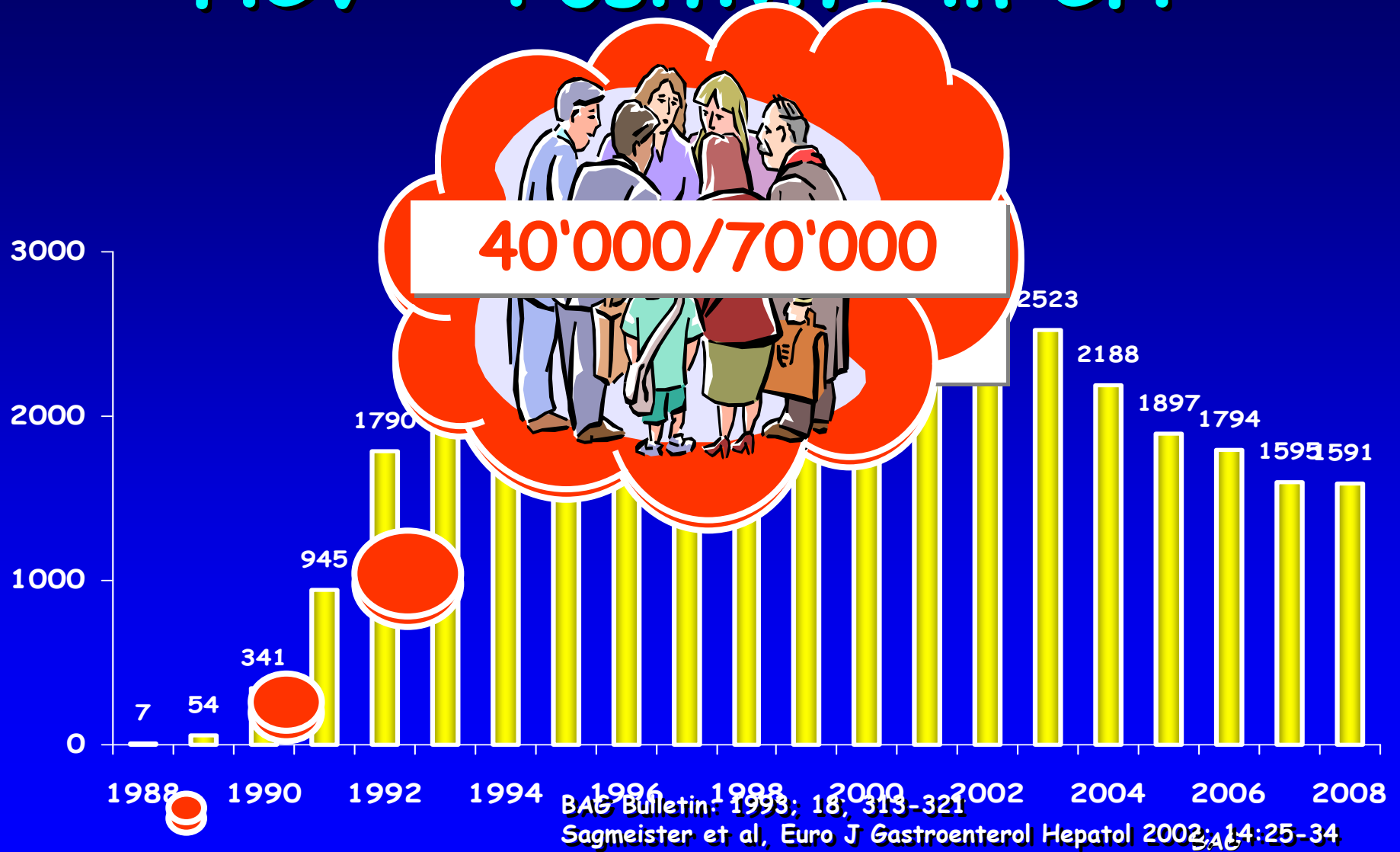
Helbling et al., Hepatology 2002;35:447-54

Hepatitis C Prevalence

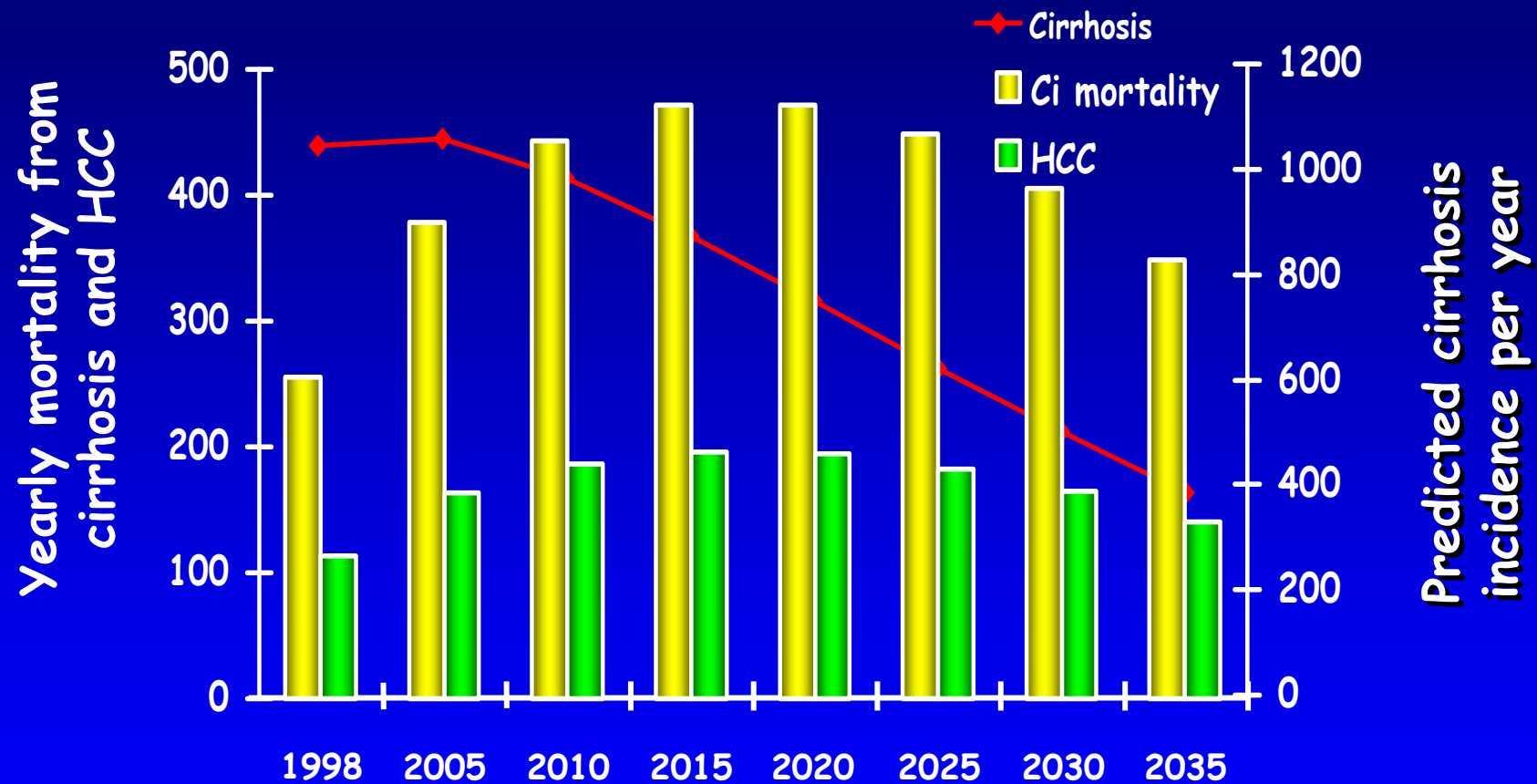


Modi et al. Hepatology 2000

HCV - Positivity in CH

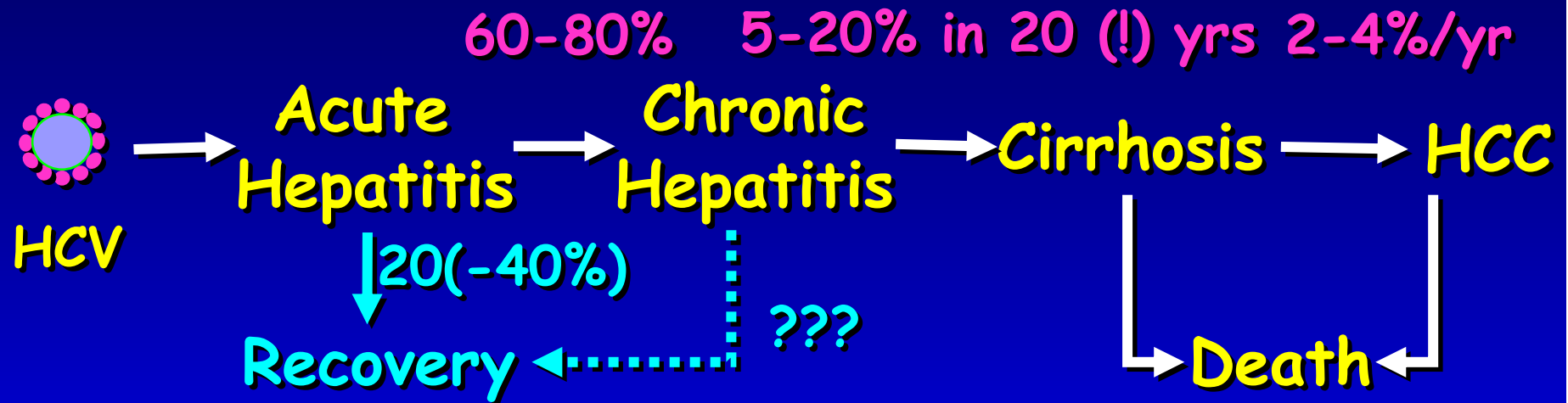


Hepatitis C - Trends for CH



Sagmeister et al, Eur J Gastroent Hepatol 2002; 14:25-34

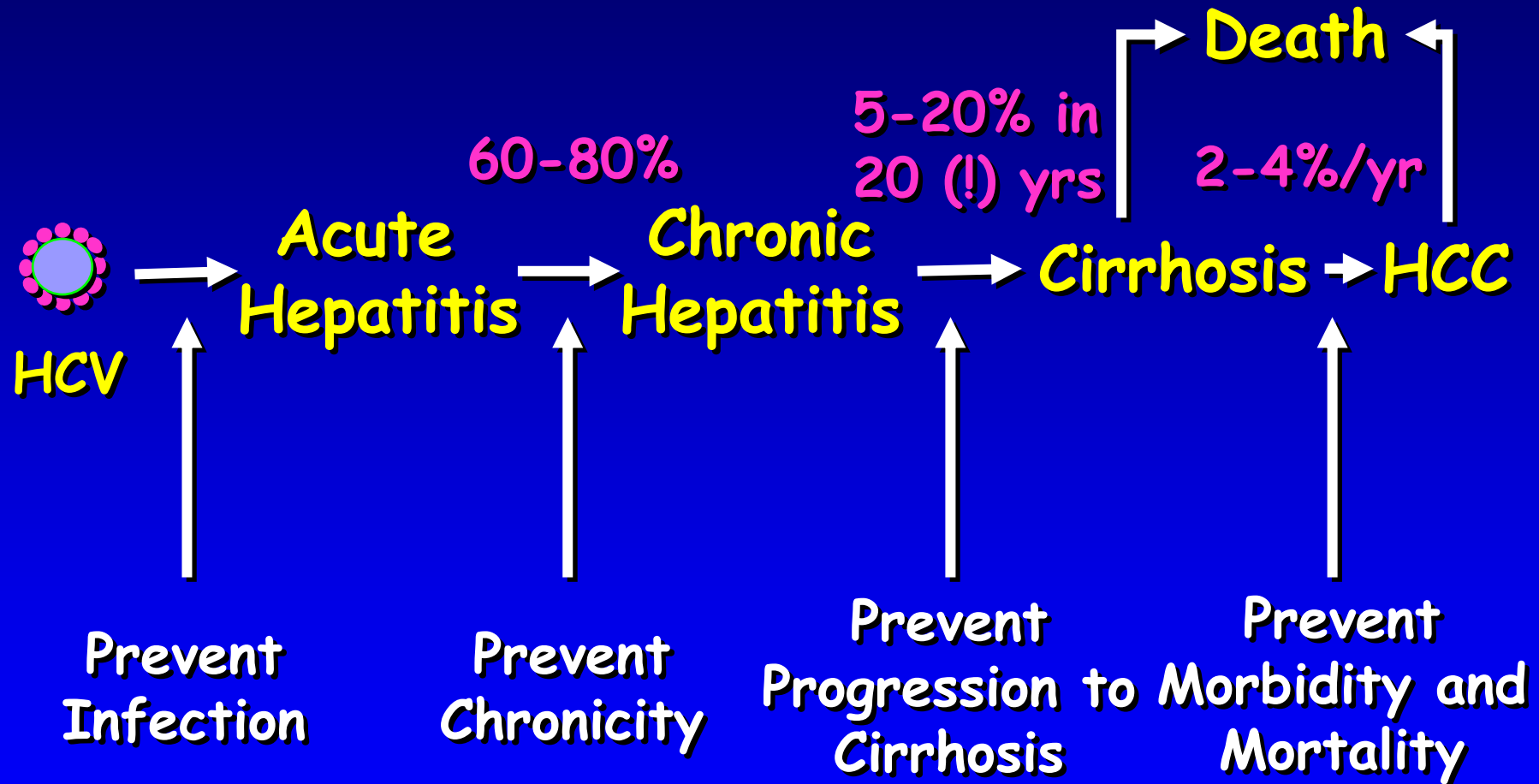
Natural history of HCV infection



Predictive Factors for Fibrosis Progression

- Alcohol (<20g female; <30g male?), Cannabis, Tobacco
- Age at infection (>40 yrs.?)
- Co-infektion (HIV, HBV)
- Higher Grading and Staging at diagnosis
- Men
- Steatosis/Overweight/Insulin resistance
- Immunodeficiency
- Iron Overload

Natural history of HCV infection



Who should be tested?

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.
- Persons with conditions associated with a high prevalence of HCV infection including:
 - Persons with HIV infection
 - Persons with hemophilia who received clotting factor concentrates prior to 1987
 - Persons who have ever been on hemodialysis
 - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants prior to July 1992 including:
 - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
 - Persons who received a transfusion of blood or blood products
 - Persons who received an organ transplant
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons*

Ghany et al Hepatology 2009;49:1335-1374

Suspicion of HCV-Infection

RIBA:

Given the widespread availability of nucleic acid testing, the role for RIBA testing in HCV diagnosis and management has all but disappeared

HCV Antigen

2. Molecular Assays

- Qualitative
- Quantitative

3. Genotype

Interpretation of HCV Assays

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low-level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

Liver biopsy

Grading = inflammatory activity

Staging = Degree of fibrosis

Other diagnosis

Non invasive markers of fibrosis

APRI: AST to platelet ratio index
 $(AST/ULN)/Tc \times 100$

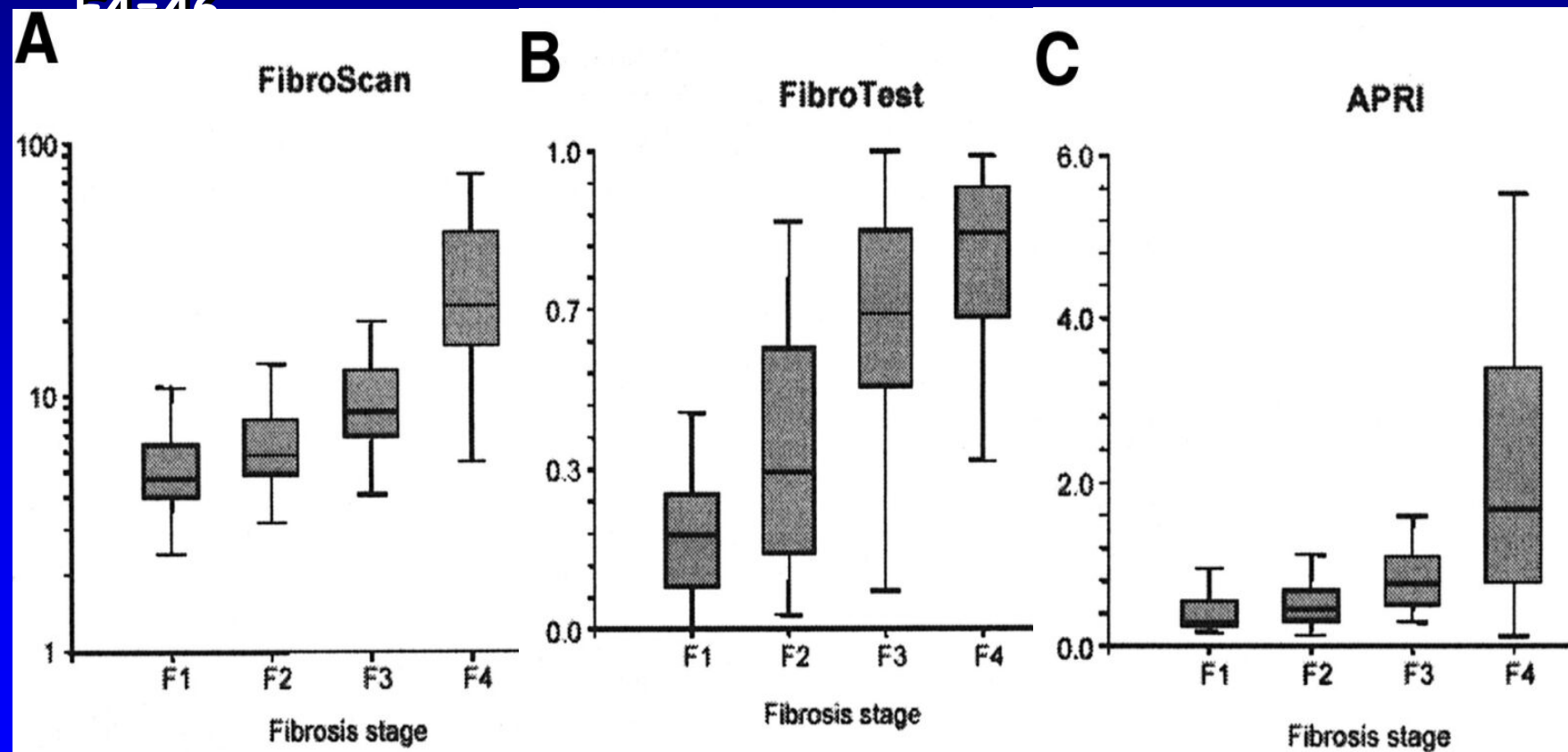
Fibrotest: alfa2-macroglobulin, haptoglobin,
gamma-GT, Bili, apolipoprotein-A1

Fibroscan



Fibroscan, Fibrotest, APRI and Biopsy

- Prospektive Study in 183 Pts with CHC F1=47, F2=52, F3=37, F4=46

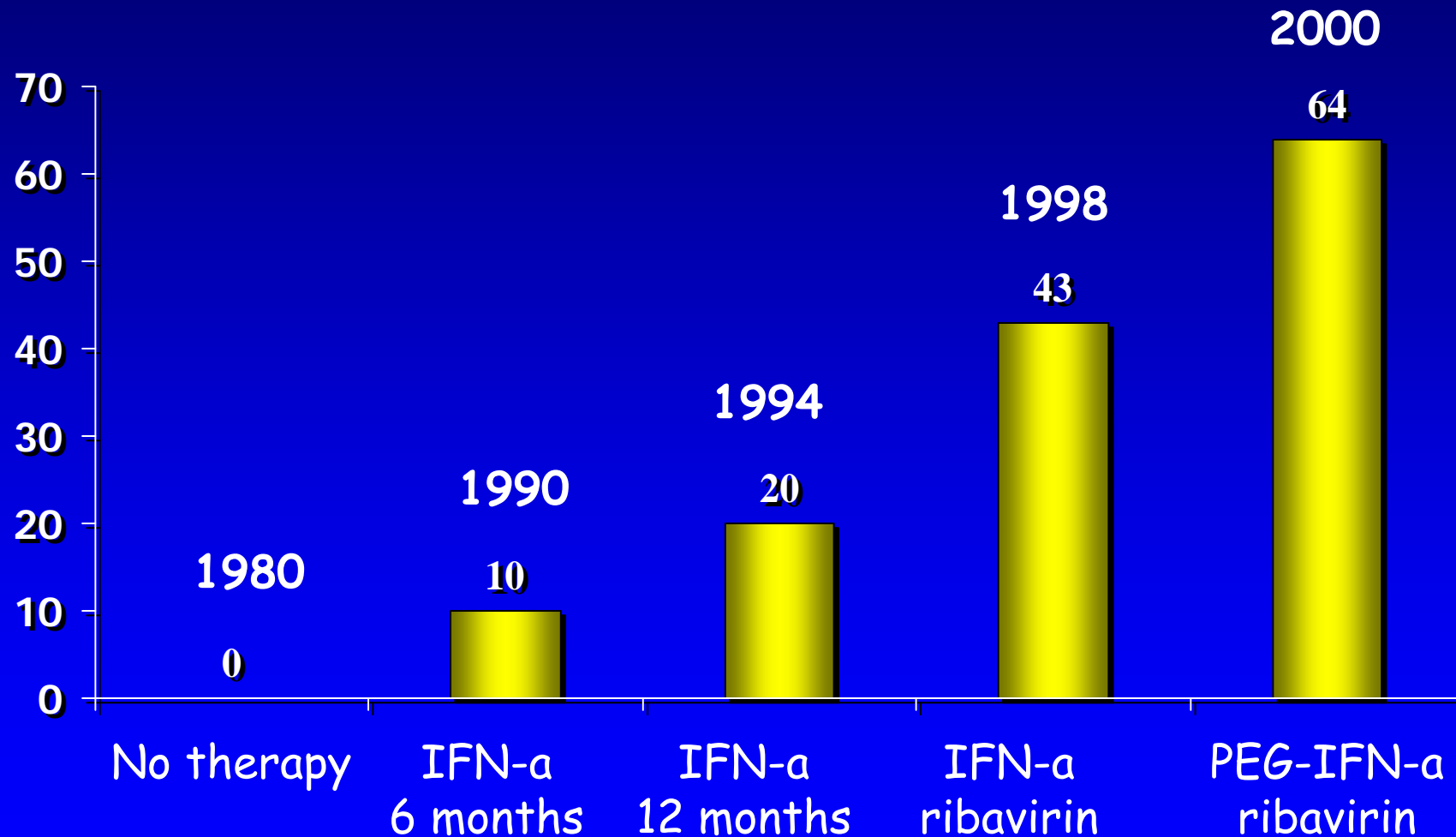


Castera et al Gastroenterology 2005;128:343-50

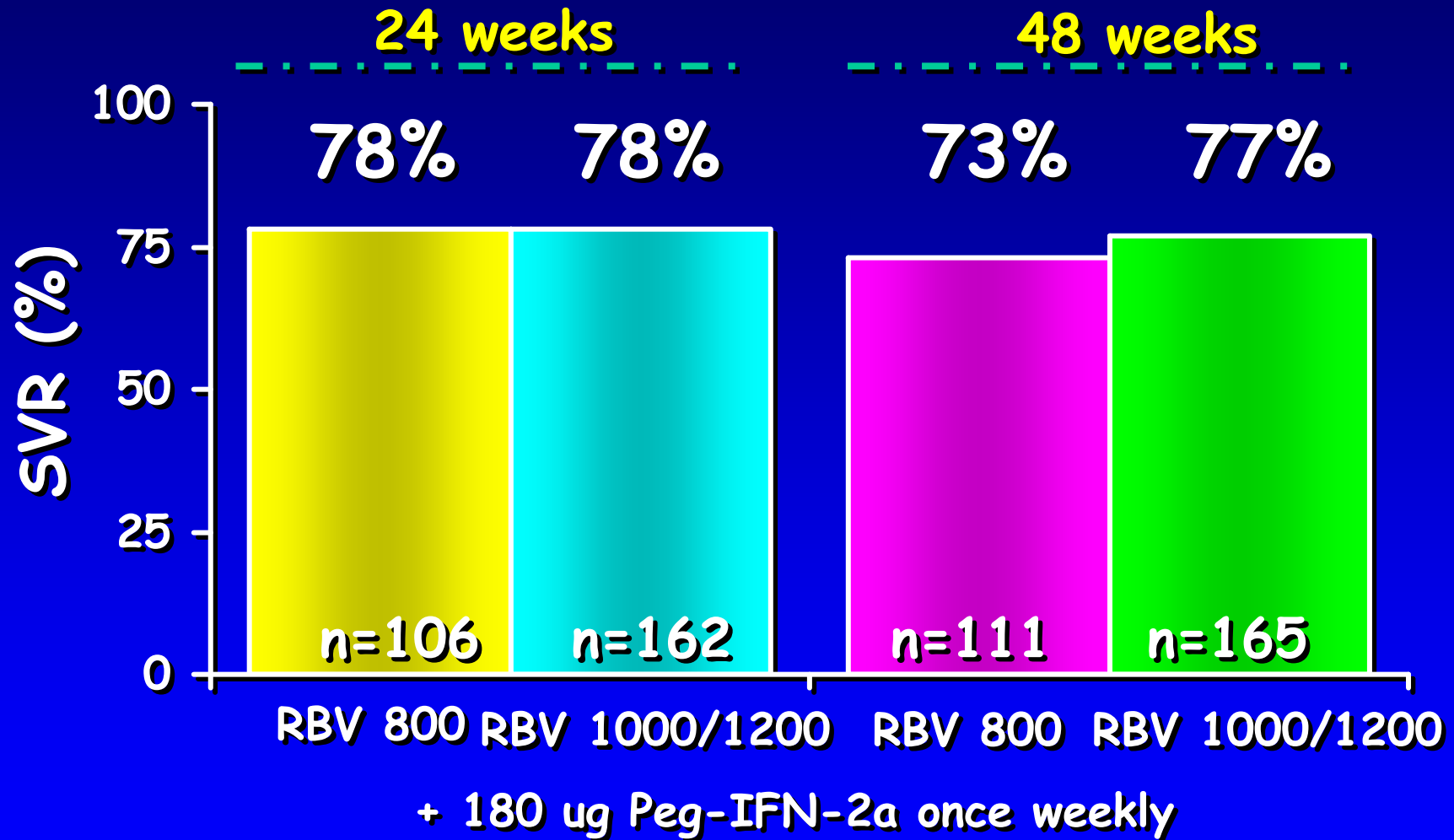
Indications for treatment

- (elevated liver enzymes > 6 Monate)
- HCV RNA positive
- Fibrosis Score (\geq F2 (Metavir), \geq F3 (Ishak))
 - Genotyp I
- Compliance
- No significant contraindication

Treating chronic hepatitis C: the evolution

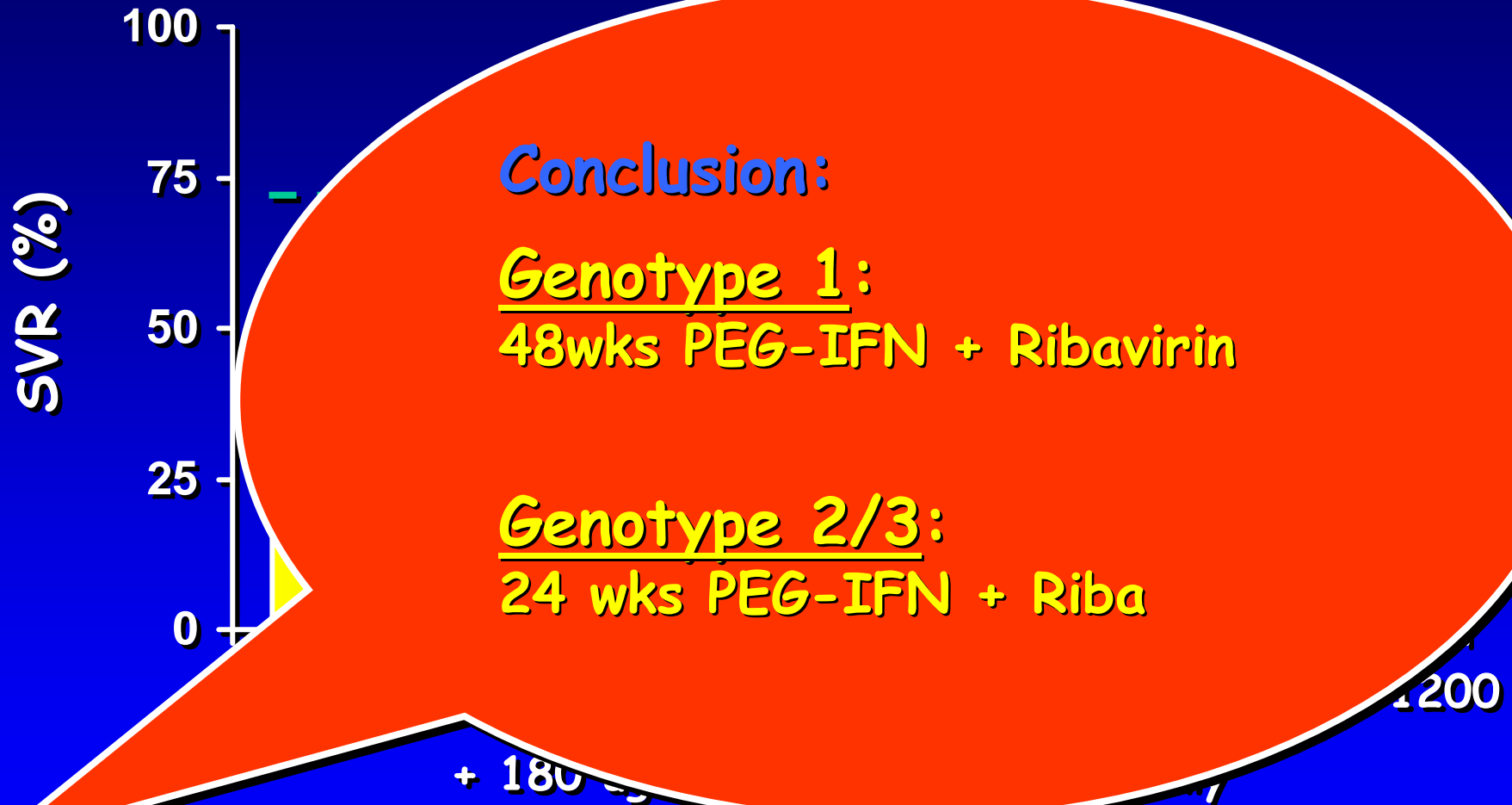


Efficacy: Genotype Non-1



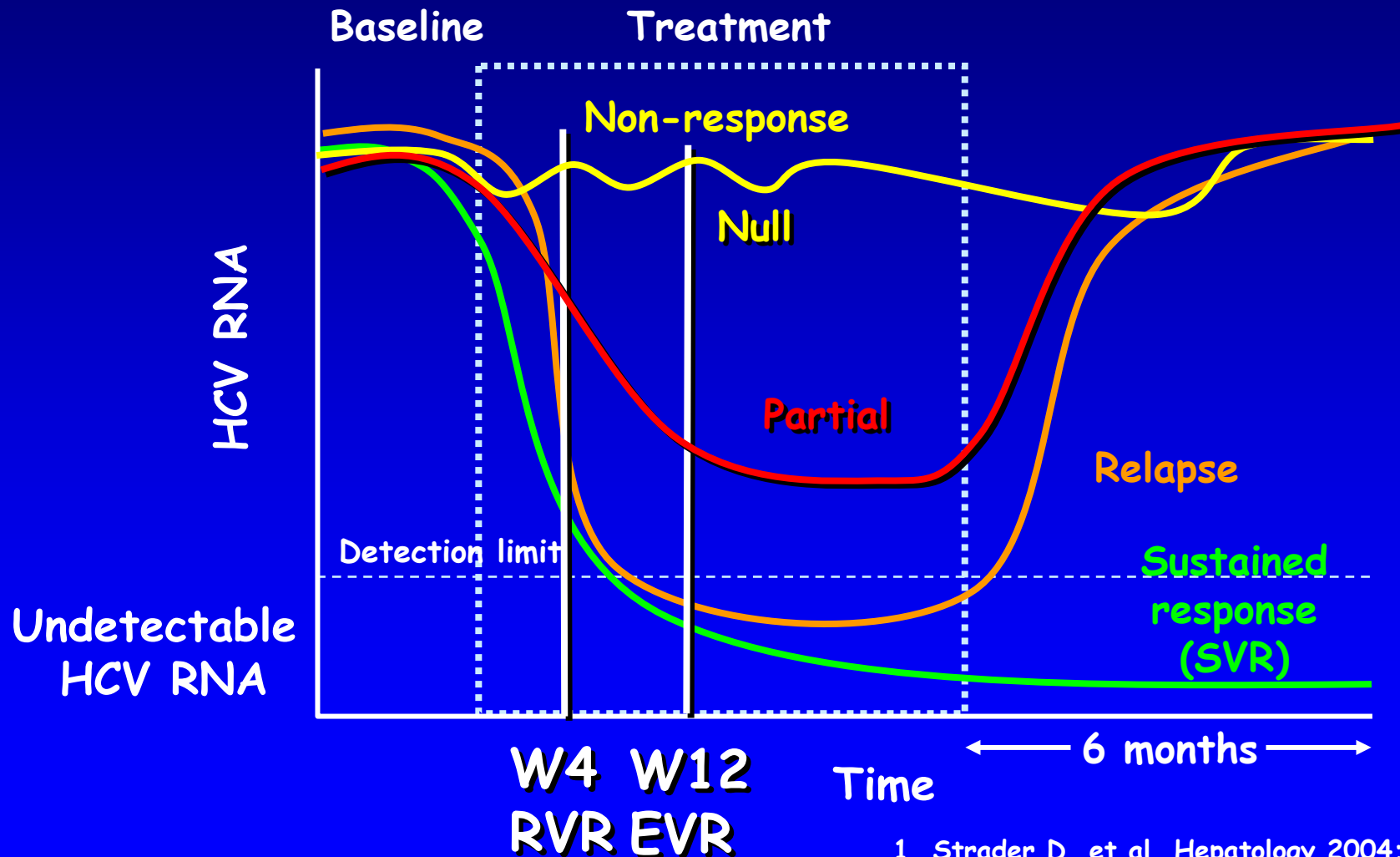
Hadziyannis et al. Ann Intern Med 2004;140:346-55

Efficacy: Genotype 1



Hadziyannis et al. Ann Intern Med 2004;140:346-55

Patterns of virological response

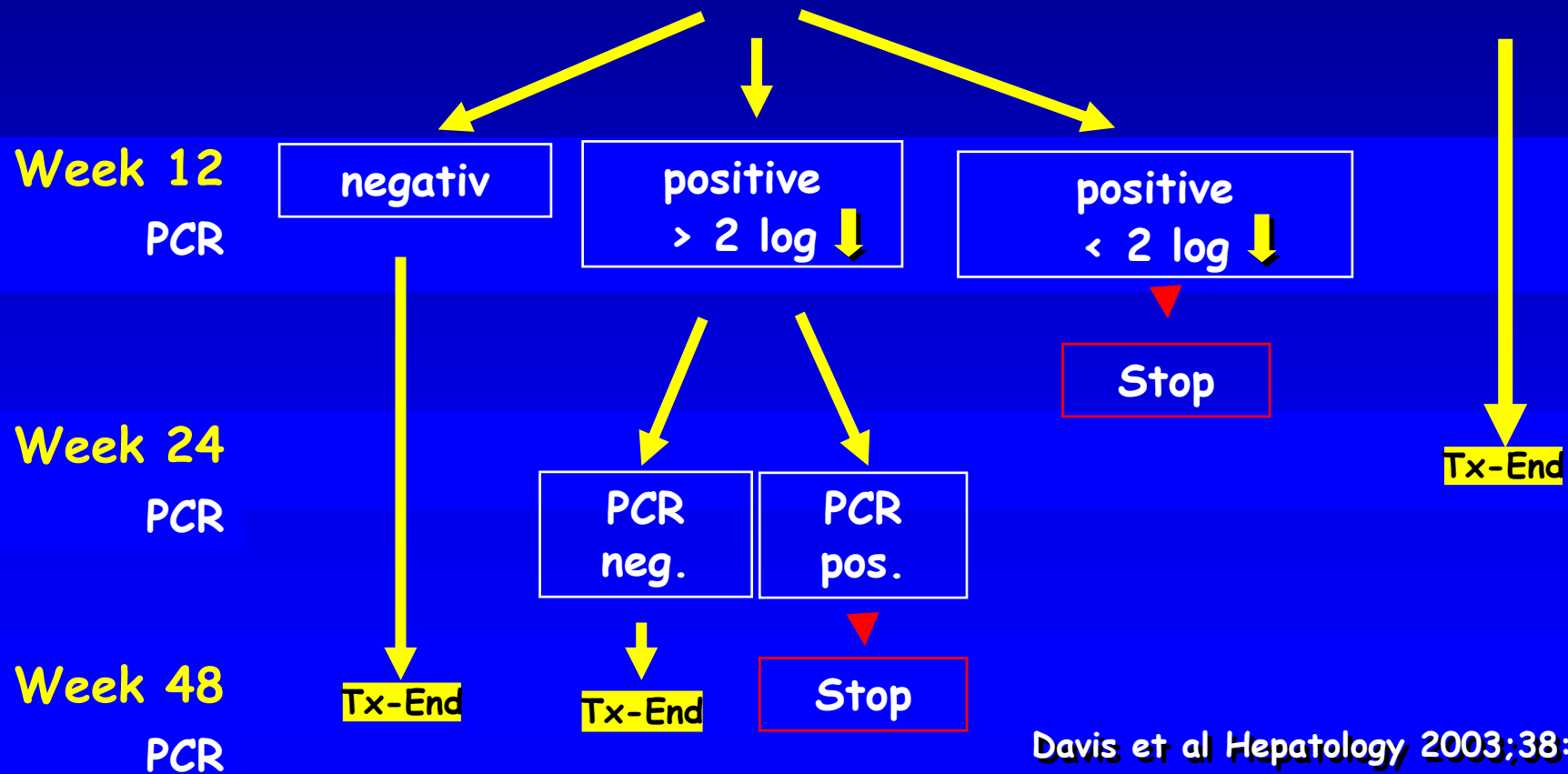


1. Strader D, et al. Hepatology 2004; 39: 1147

Chronic Hepatitis C - Therapeutic algorithm

Genotype 1
PEG-IFN + Ribavirin

Genotype 2/3
PEG-IFN + Ribavirin



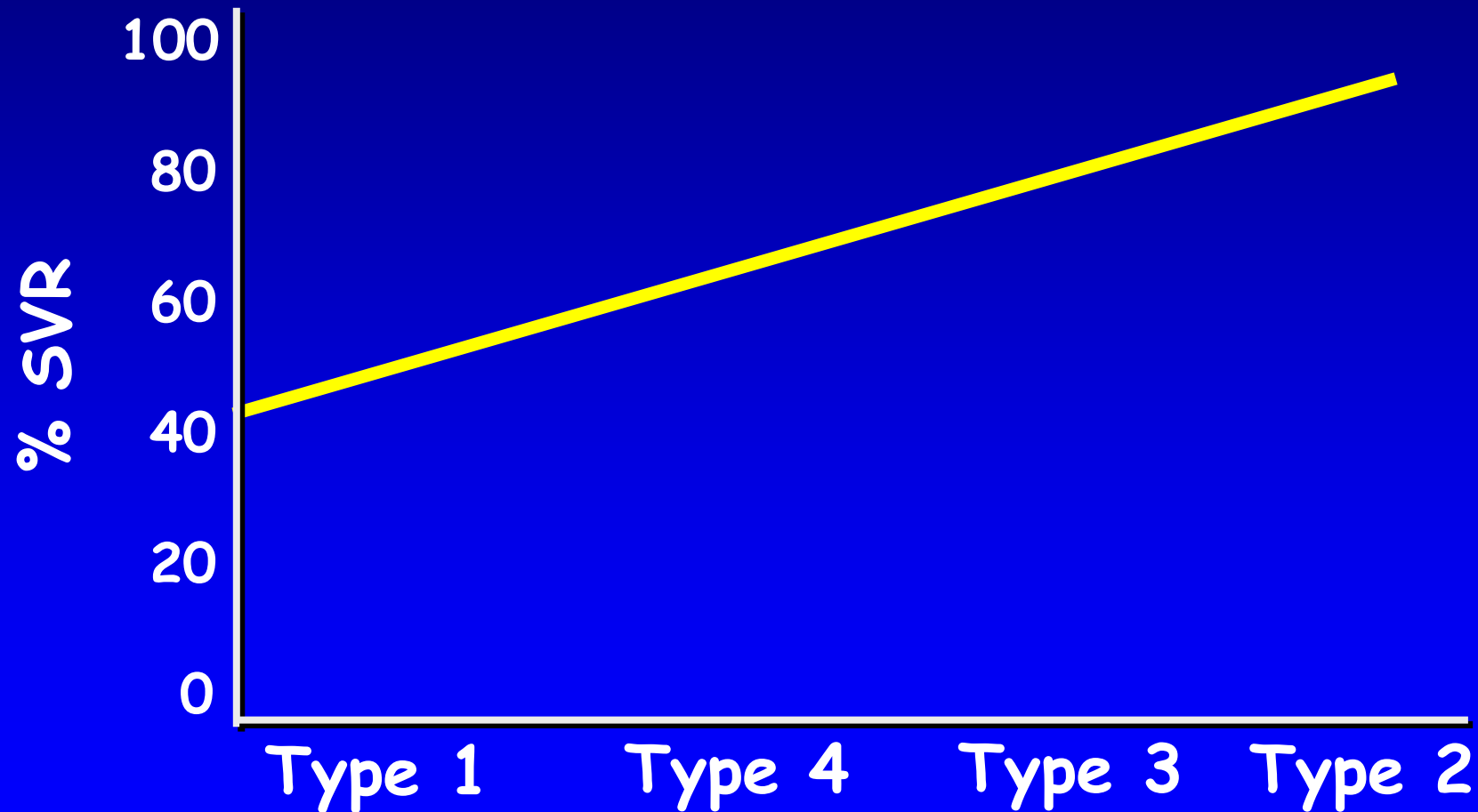
Davis et al Hepatology 2003;38:645-52

Predictive factors

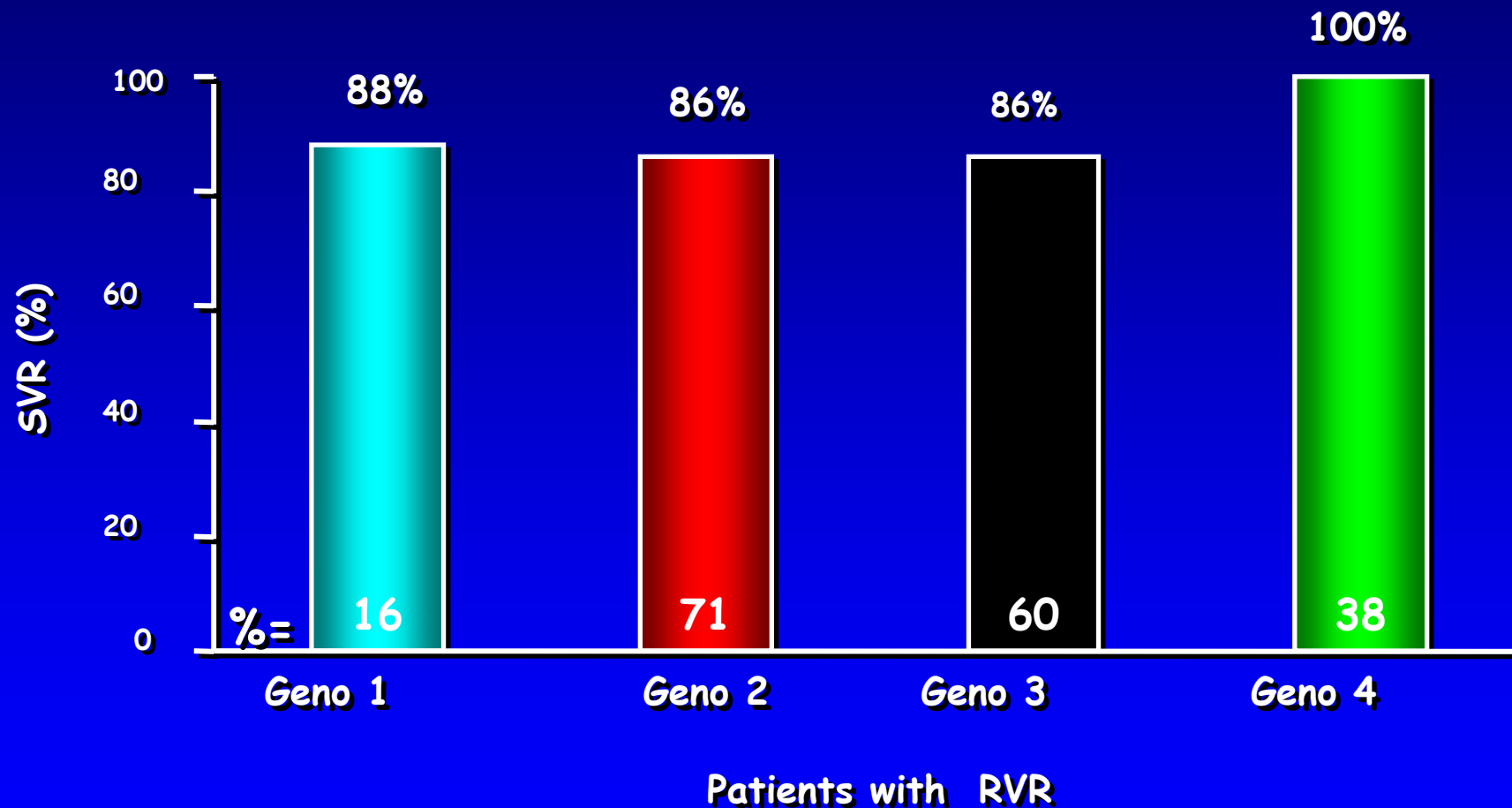
- Genotype
- Degree of fibrosis
- Insulin resistance/Steatosis
- Age
- Ethnicity
- Viral load
- Body weight
- Sex
- Adherence
- Alcohol

SVR

Effect of HCV genotype

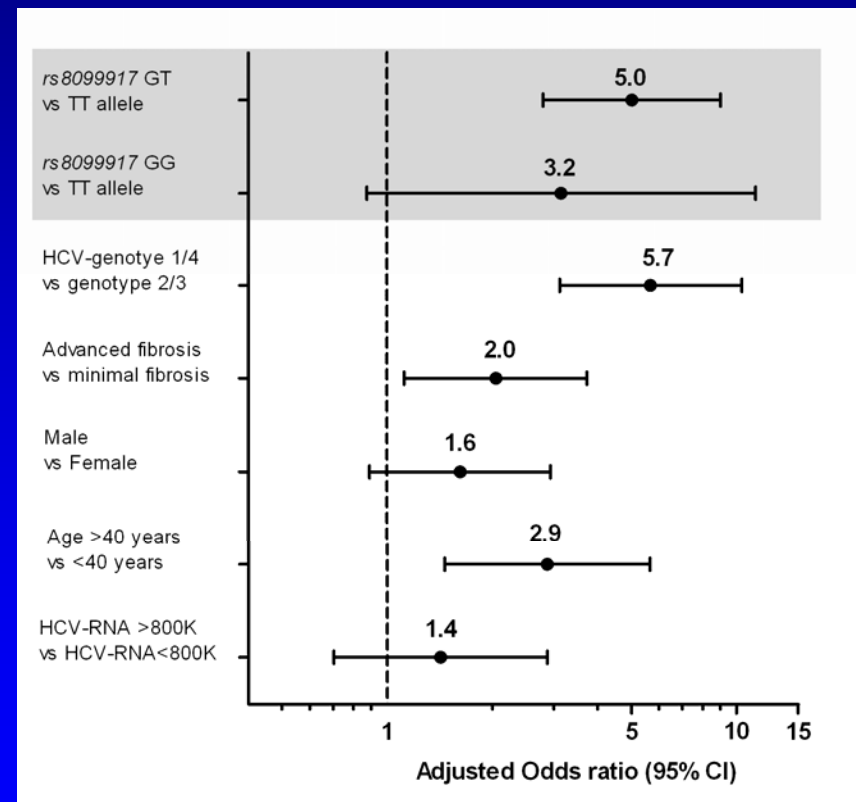
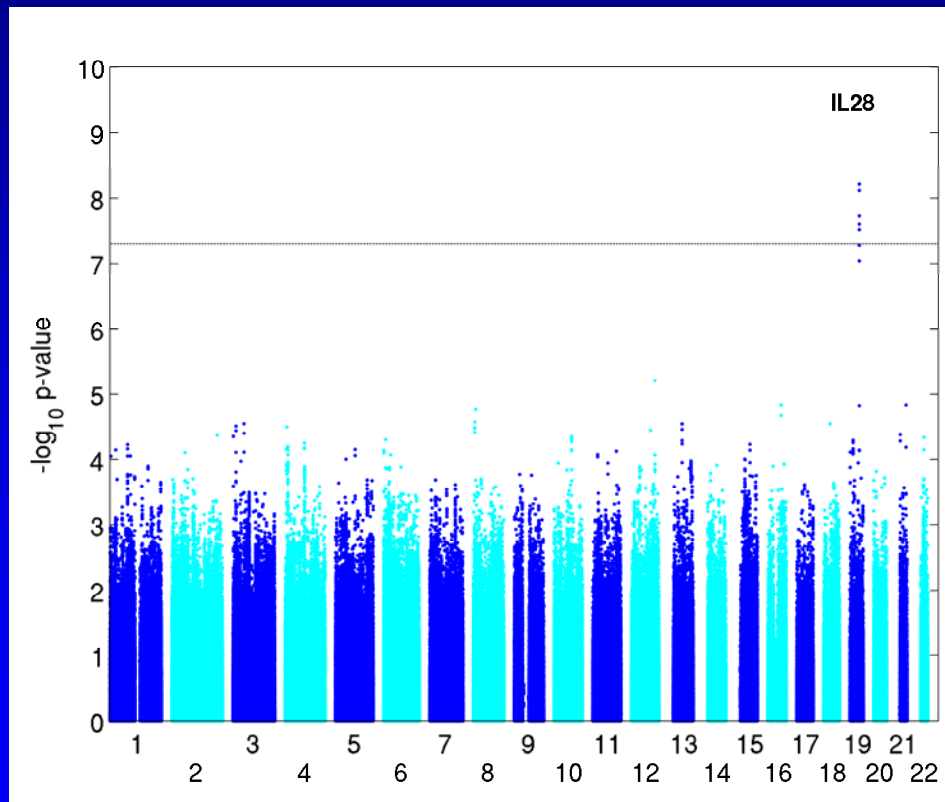


RVR as predictor for SVR



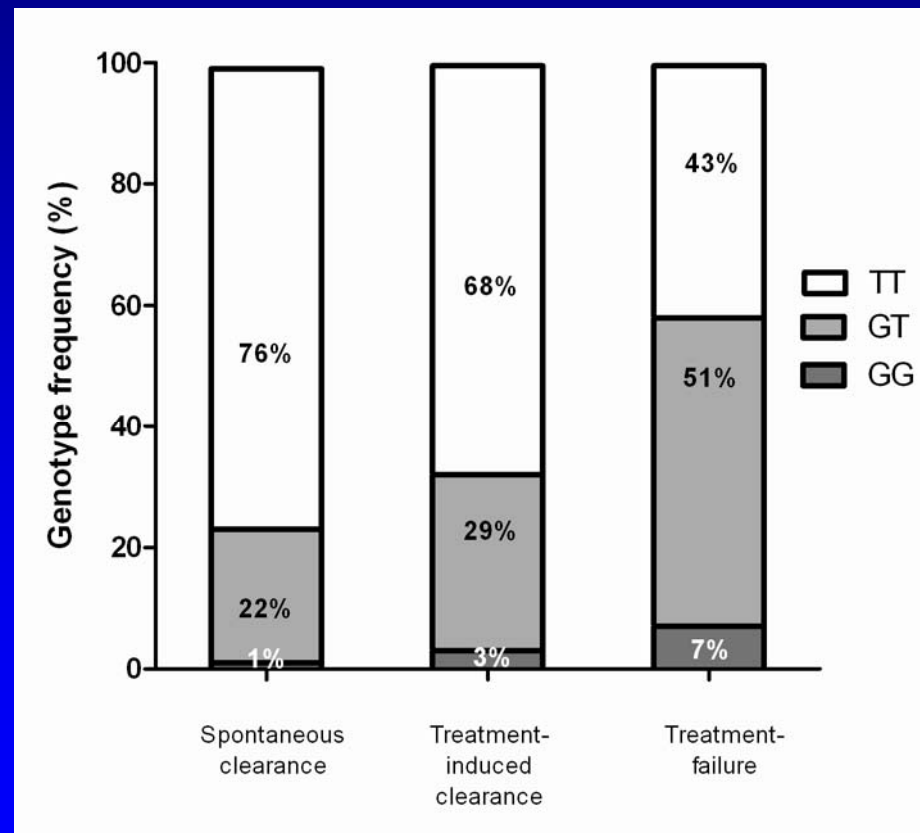
Fried et al: J Hepatol 2008 Abstract 991

IL 28 Polymorphism



Bochud et al Gastroenterol in press

IL 28 Polymorphism



Bochud et al Gastroenterol in press

Special patient population

Normal Transaminases

Acute Hepatitis C

Non-Responders

Liver cirrhosis

Renal failure

HCV-HIV-Co-Infektion

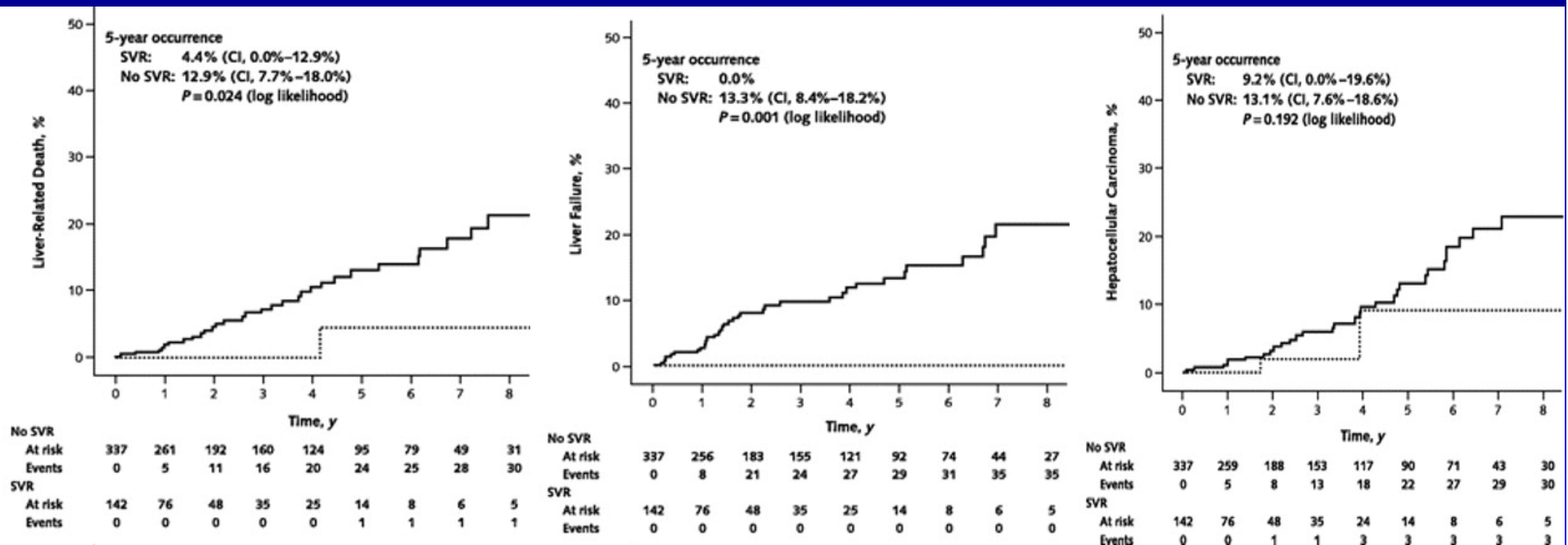
After OLT

Children

Extrahepatic manifestations

Effect of SVR on natural history

470 Pts with Ishak Score 4-6

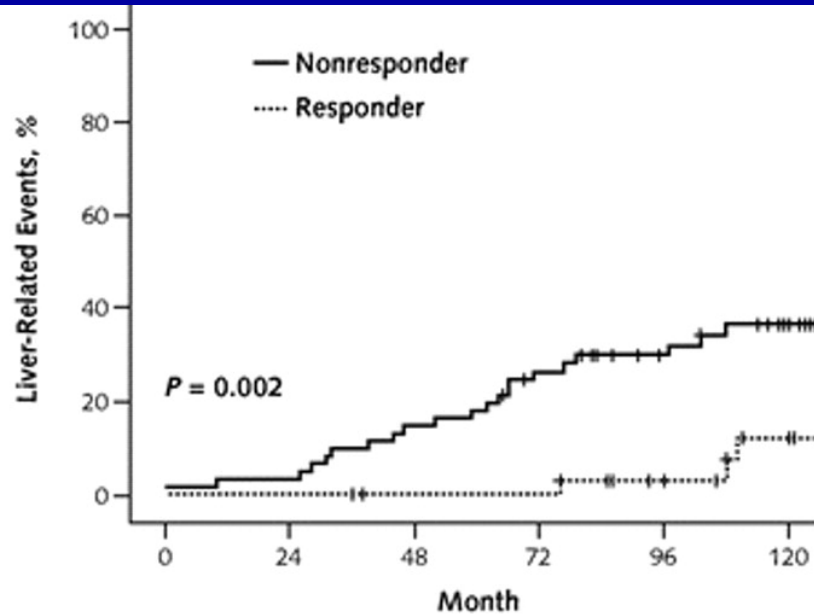


Veldt et al: Ann Intern Med 2007;147:677-84

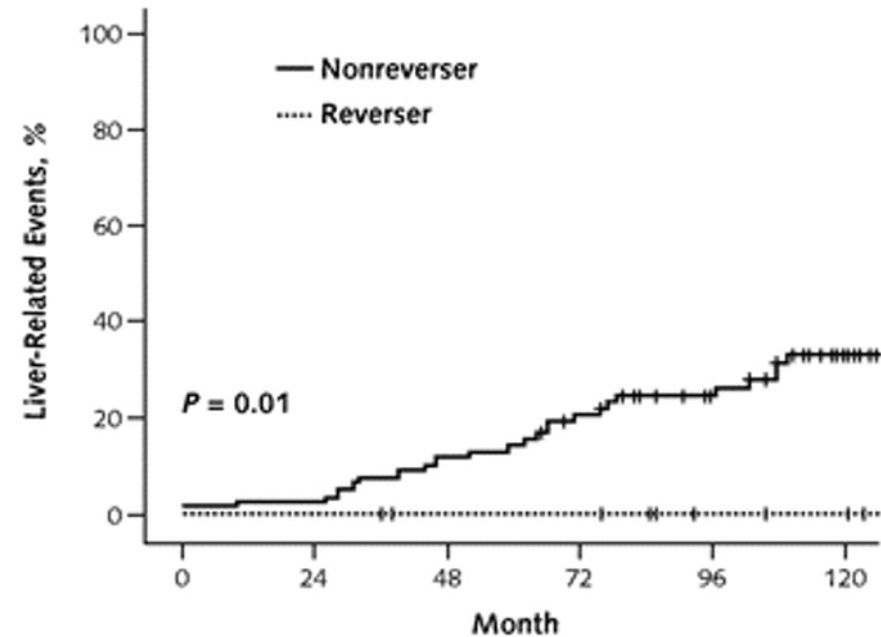
Regression of cirrhosis

n=96; HCV Zirrhose und INF Therapie (meistens mono)
 Follow-up Bx nach Therapie; Zirrhoseregression (\leq F2)

SVR: 39 (41%) pts
Zirrhoseregression: 18 pts (17 SVR)



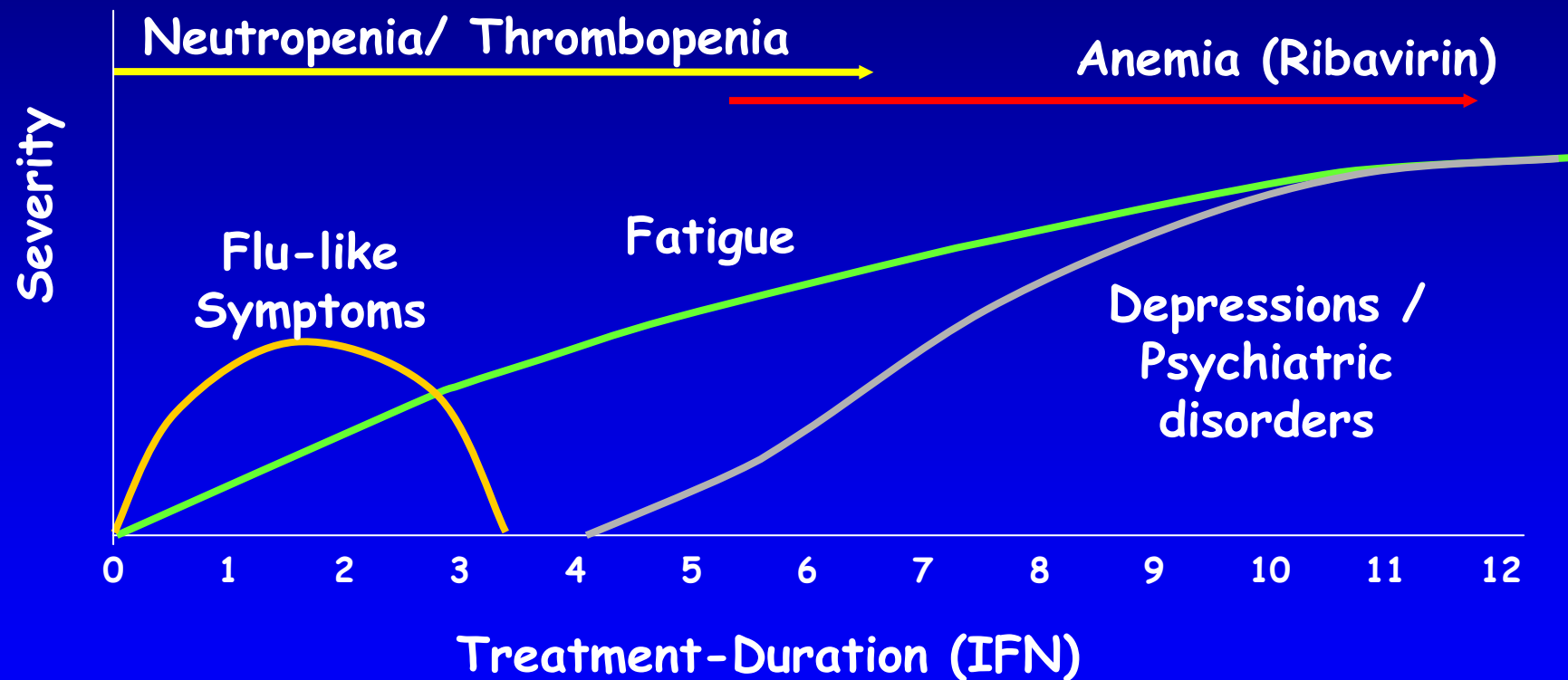
Number at risk		0	24	48	72	96	120
Nonresponders	61	59	52	43	32	22	
Responders	35	35	33	33	27	18	



Number at risk		0	24	48	72	96	120
Nonreversers	78	76	69	60	47	30	
Reversers	18	18	16	16	12	10	

Mallet et al Ann Intern Med 2008;149:399-403

Nebenwirkungen Interferon/Ribavirin Therapie



Nebenwirkungsmanagement

- **Grippale Symptome**
 - Paracetamol
- **Dosisreduktion bei Blutbildveränderungen**
 - Im Einzelfall Erythropoetin/Neupogen
- **Depression**
 - Selektive Serotonin Wiederaufnahmehemmer (SSRI)
- **Suizidgefahr**
 - Therapieabbruch und Hospitalisierung
- **Interferon-induzierte Schilddrüsenerkrankungen**
 - In der Regel kein Grund für Therapieabbruch
 - Werden in Abhängigkeit von der Schilddrüsenfunktion behandelt

Maintenance Therapy HALT-C

- RCT in 1050 pts with HCV and fibrosis \geq Ishak 3, CTP \leq 6
- PEG-INF2a 90ug vs Control
- Follow-up: 3.5

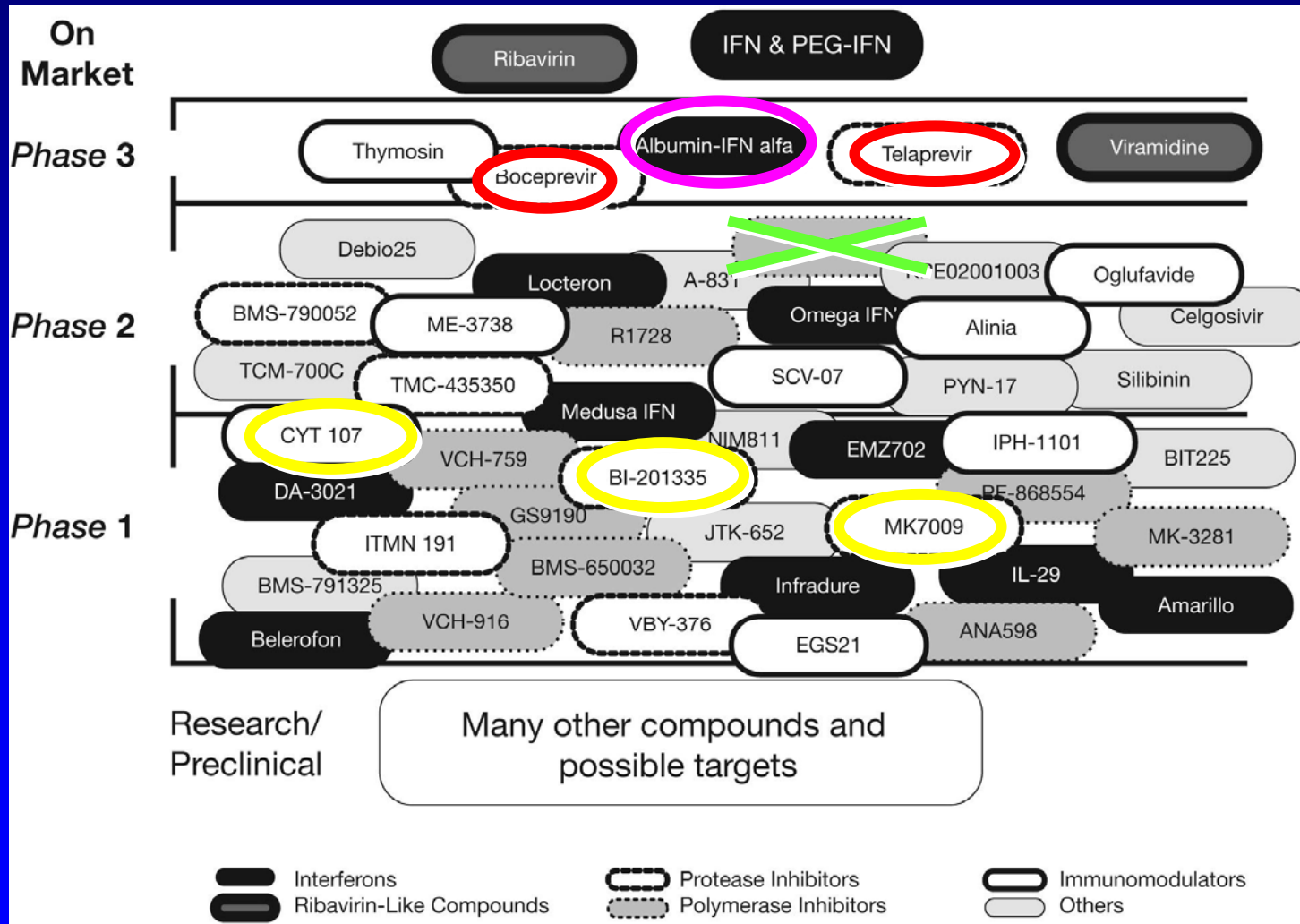
	Death	Decompensation	HCC	Fibrosis progression
PEG	6.6	14.3	2.8	28.2
Control	4.6	13.2	3.2	31.9

Di Bisceglie et al N Engl J Med 2008;359:2429-41

Lok et al Gastroenterol 2009;136:138-148

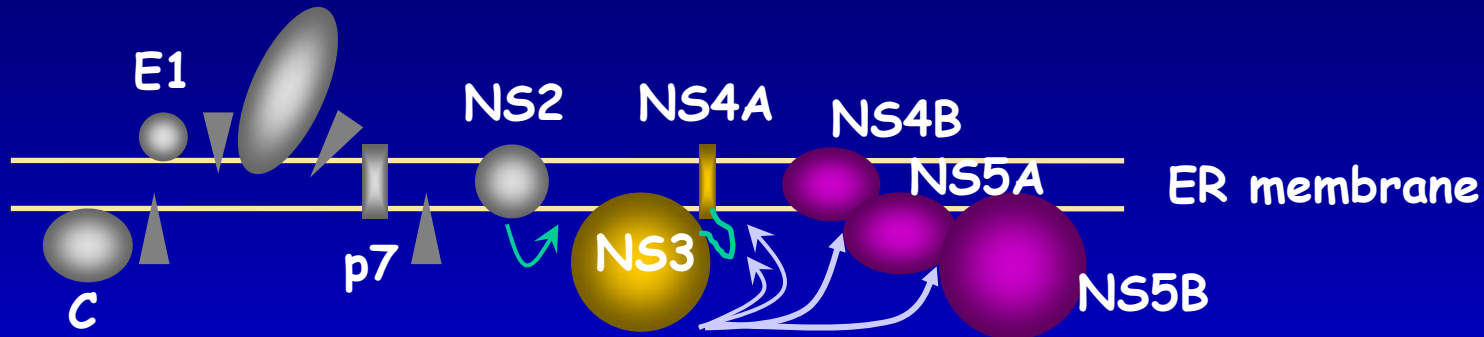
Hepatitis C

Neue Substanzen



Hepatitis C

Neue Substanzen



Protease
Inhibitoren

Polymerase
Inhibitoren

*Specifically Targeted Antiviral Therapy for
Hepatitis C (STAT-C)*

New Area

ORIGINAL ARTICLE

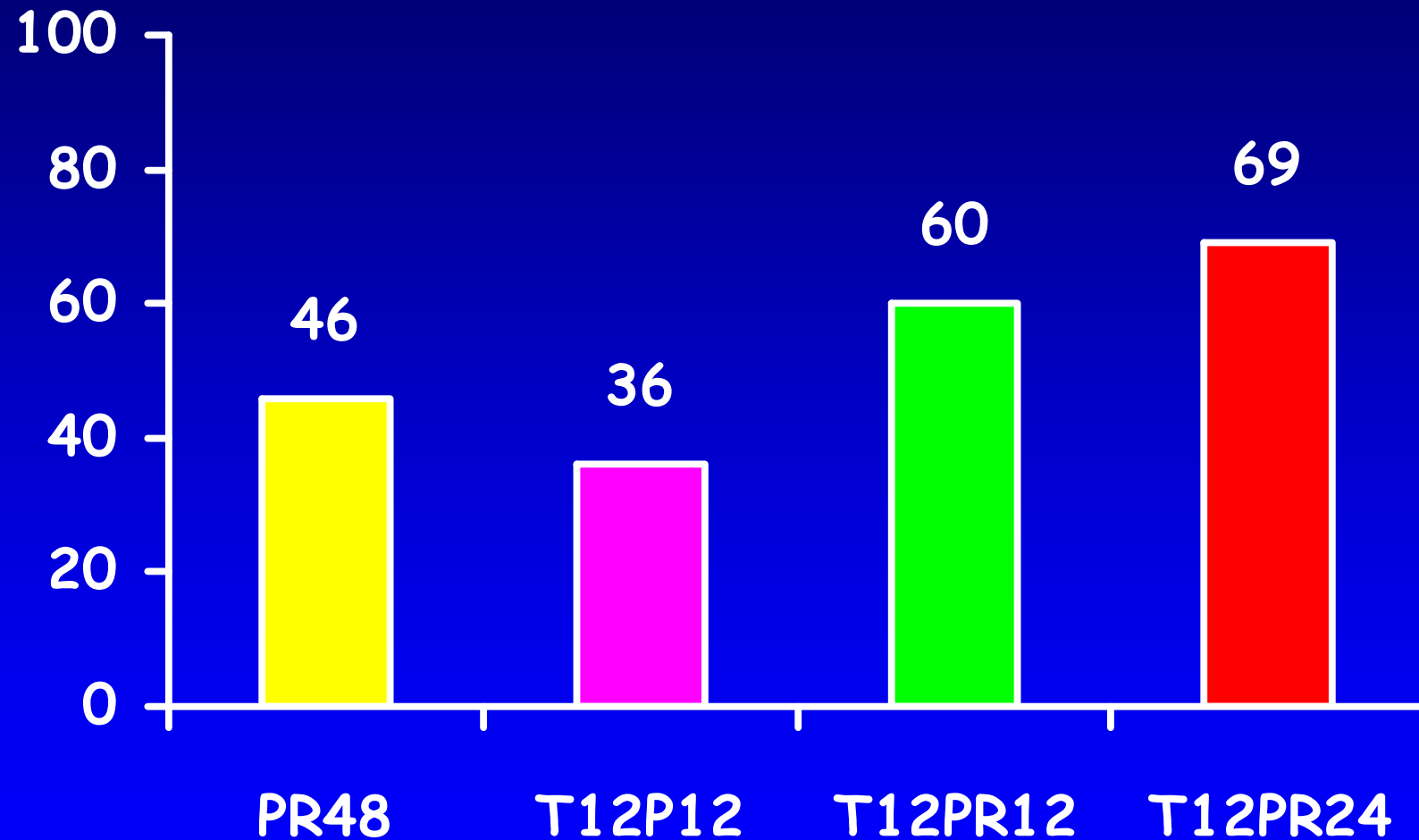
Telaprevir and Peginterferon with or without Ribavirin for Chronic HCV Infection

Christophe Hézode, M.D., Nicole Forestier, M.D., Geoffrey Dusheiko, M.D., Peter Ferenci, M.D., Stanislas Pol, M.D., Tobias Goesser, M.D., Jean-Pierre Bronowicki, M.D., Marc Bourlière, M.D., Shahin Gharakhanian, M.D., Leif Bengtsson, B.S.C., Lindsay McNair, M.D., M.P.H., Shelley George, M.D., Tara Kieffer, Ph.D., Ann Kwong, Ph.D., Robert S. Kauffman, M.D., Ph.D., John Alam, M.D., Jean-Michel Pawlotsky, M.D., Ph.D., and Stefan Zeuzem, M.D.,
for the PROVE2 Study Team* N Engl J Med 2009;360:1839-50.

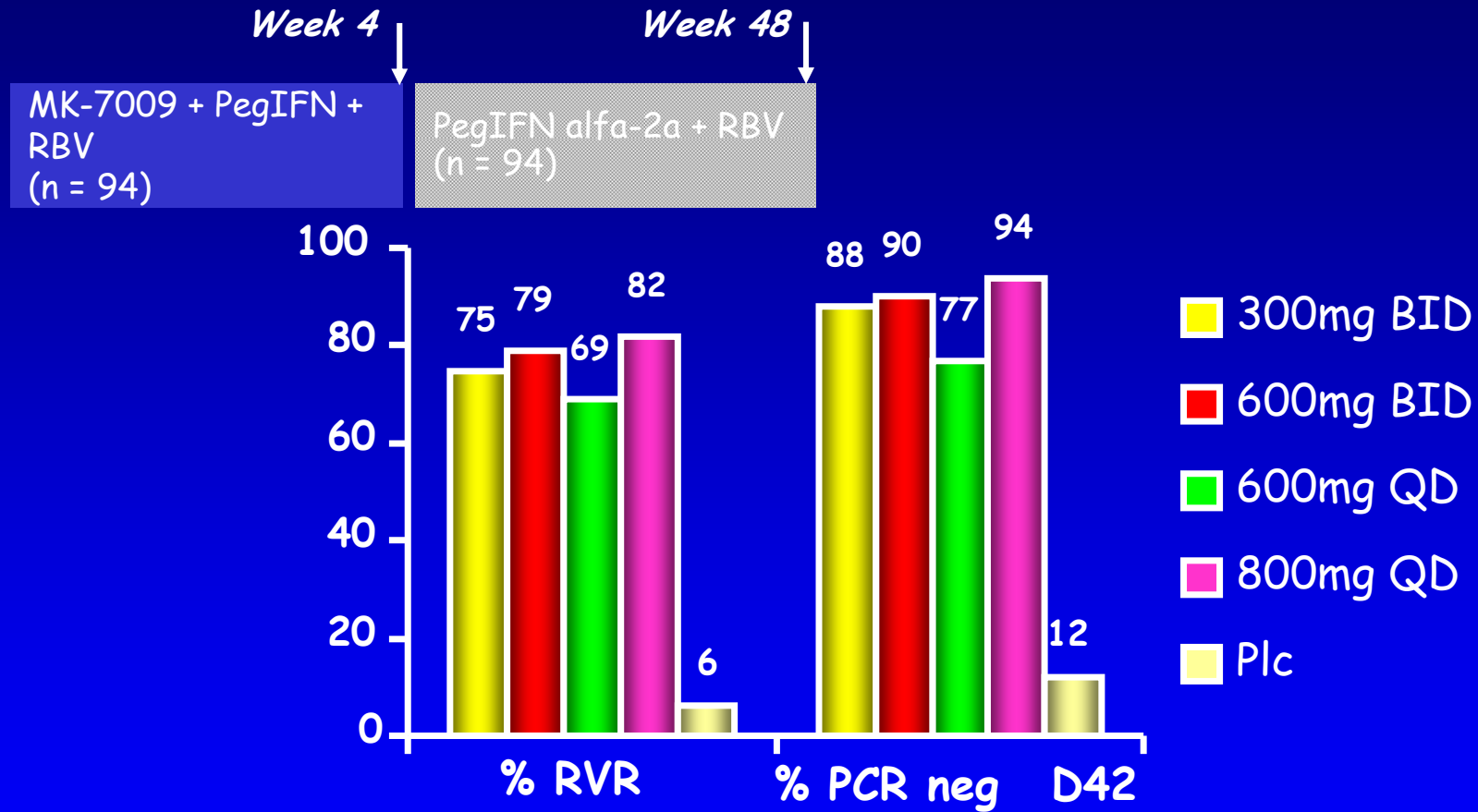
Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection

John G. McHutchison, M.D., Gregory T. Everson, M.D., Stuart C. Gordon, M.D., Ira M. Jacobson, M.D., Mark Sulkowski, M.D., Robert Kauffman, M.D., Lindsay McNair, M.D., John Alam, M.D., and Andrew J. Muir, M.D.,
for the PROVE1 Study Team* N Engl J Med 2009;360:1827-38.

New Area



MK-7009



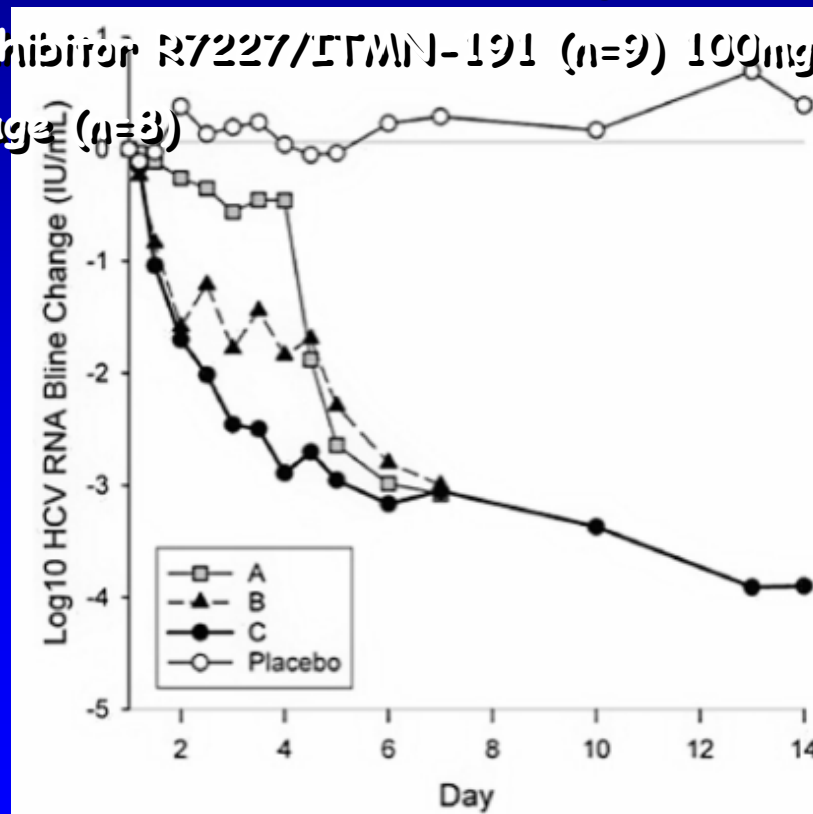
No SAE, no treatment discontinuations
Nausea and vomiting more frequent with MK-7009

Manns et al. J Hepatol 2009 50 Suppl 1: A1056

Rein orale Therapie möglich?

Inform 1

- Patienten mit Genotyp 1 (Phase)
 - A: Polymerase Inhibitor R7128 (n=8) 500mg/12h d1-3, comb. d4-7
 - B: Protease Inhibitor R7227/ETMN-191 (n=9) 100mg/8h d1-3, comb. d4-7
 - C: Comb 14 Tage (n=3)
 - Placebo (n=2)



Gane et al J Hepatol 2009 50 Suppl 1:A1046

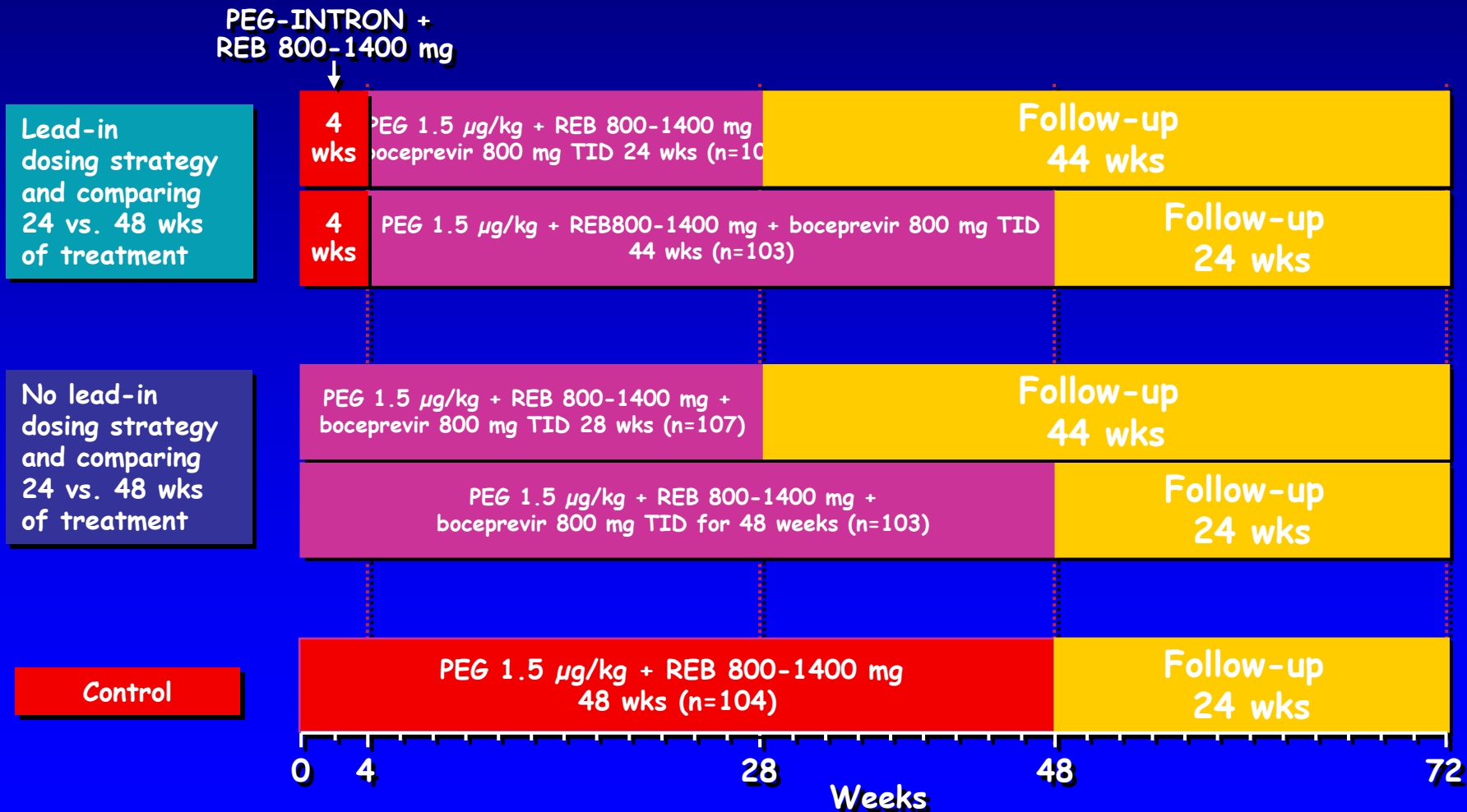
A Step Forward in Therapy for Hepatitis C

Jay H. Hoofnagle, M.D.

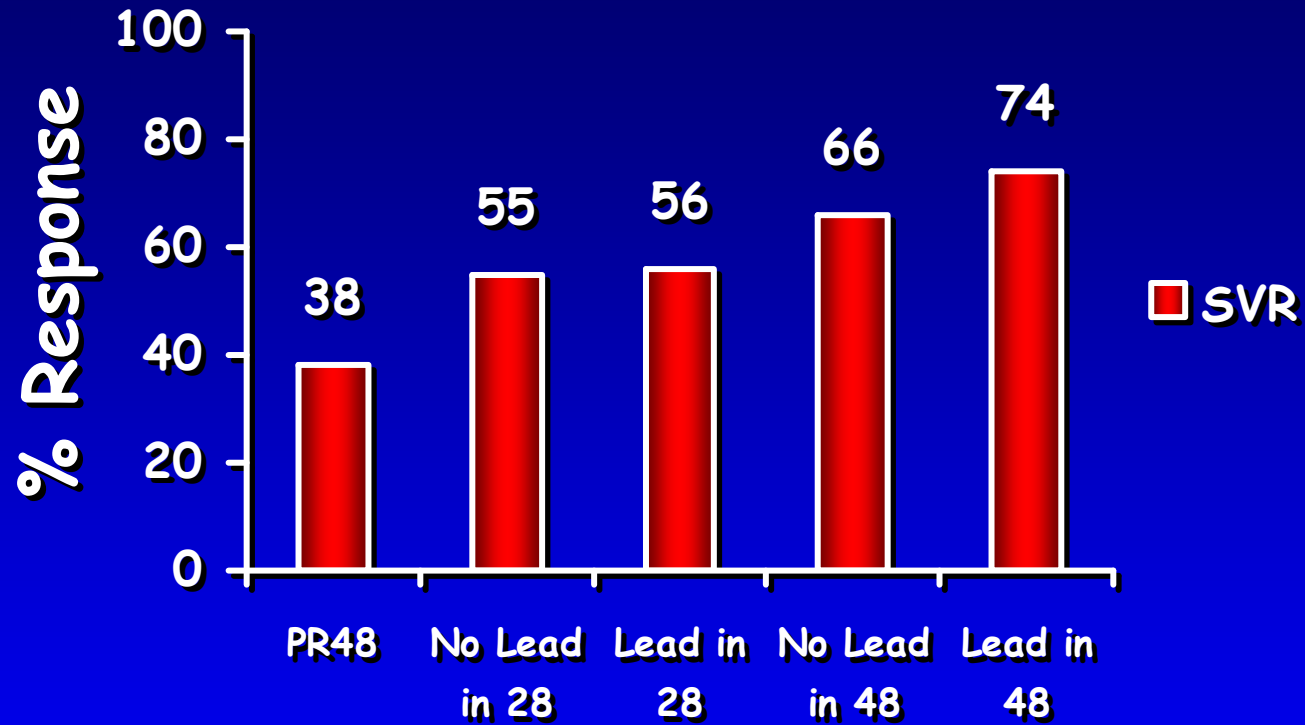


Boceprevir (Sprint-1)

- 520 behandlungsnaive Patienten mit Genotyp 1 (Phase 2)



Boceprevir (Sprint-1)



Hauptnebenwirkung
Anämie, Dysgeusie

Kwo et al J Hepatol 2009 50 Suppl 1:A