UNIVERSITÄTS KLINIKUM FRANKFURT

Hepatitis C Therapeutika

Opinion-Leader-Meeting: Therapeutische Innovationen und neue Industrie-Akademia Kooperationsmodelle

Schloss Löwenstein, Kleinheubach, 24.-25. Januar 2020

Univ.-Prof. Dr. Stefan Zeuzem
Universitätsklinikum Frankfurt a.M.

MEDIZINISCHE KLINIK 1
des Klinikums
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

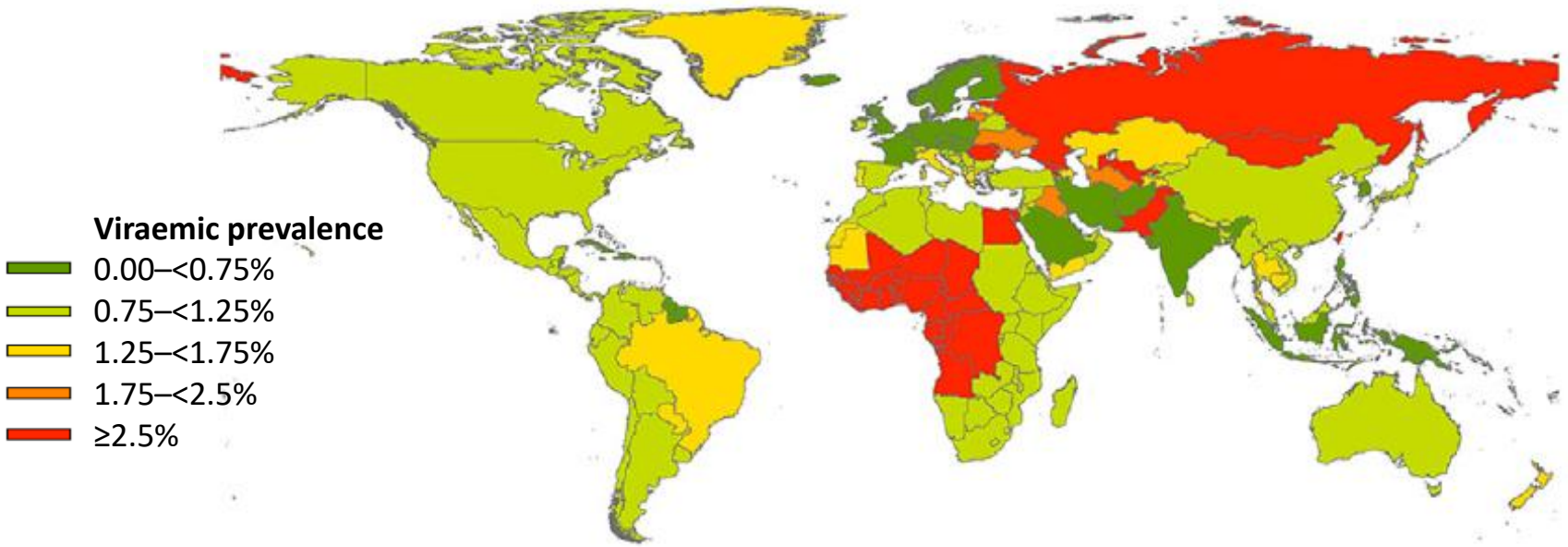
Disclosures

- Advisory boards: AbbVie, Allergan, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, Merck Sharp & Dohme/MSD
- Speaker: AbbVie, Gilead Sciences, Merck Sharp & Dohme/MSD

Epidemiology and Natural Course of Disease

Global burden of HCV

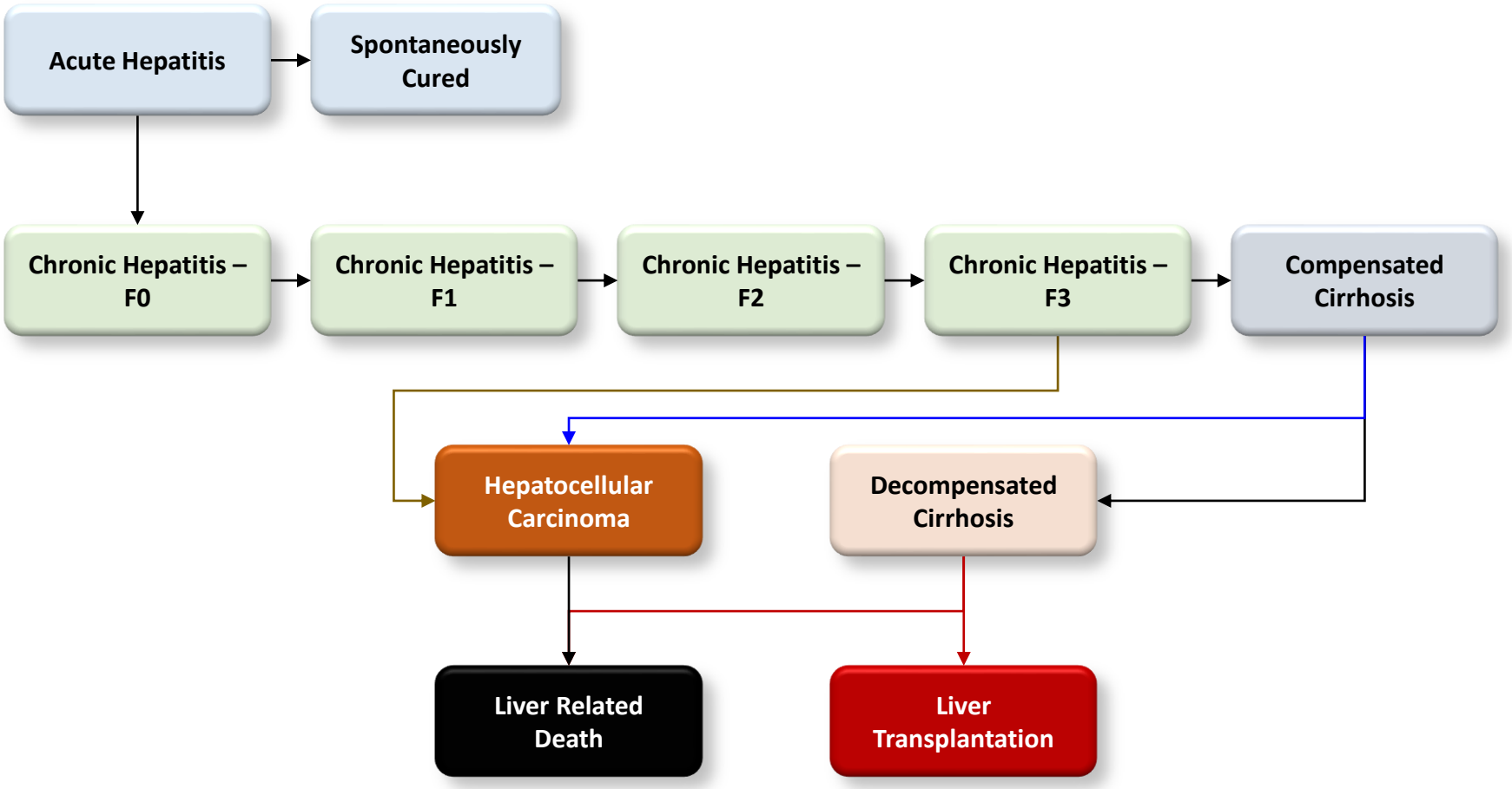
- Estimated that 80 million people are living with chronic HCV worldwide



- Annually ~700,000 people die from HCV-related complications such as cirrhosis and hepatocellular carcinoma

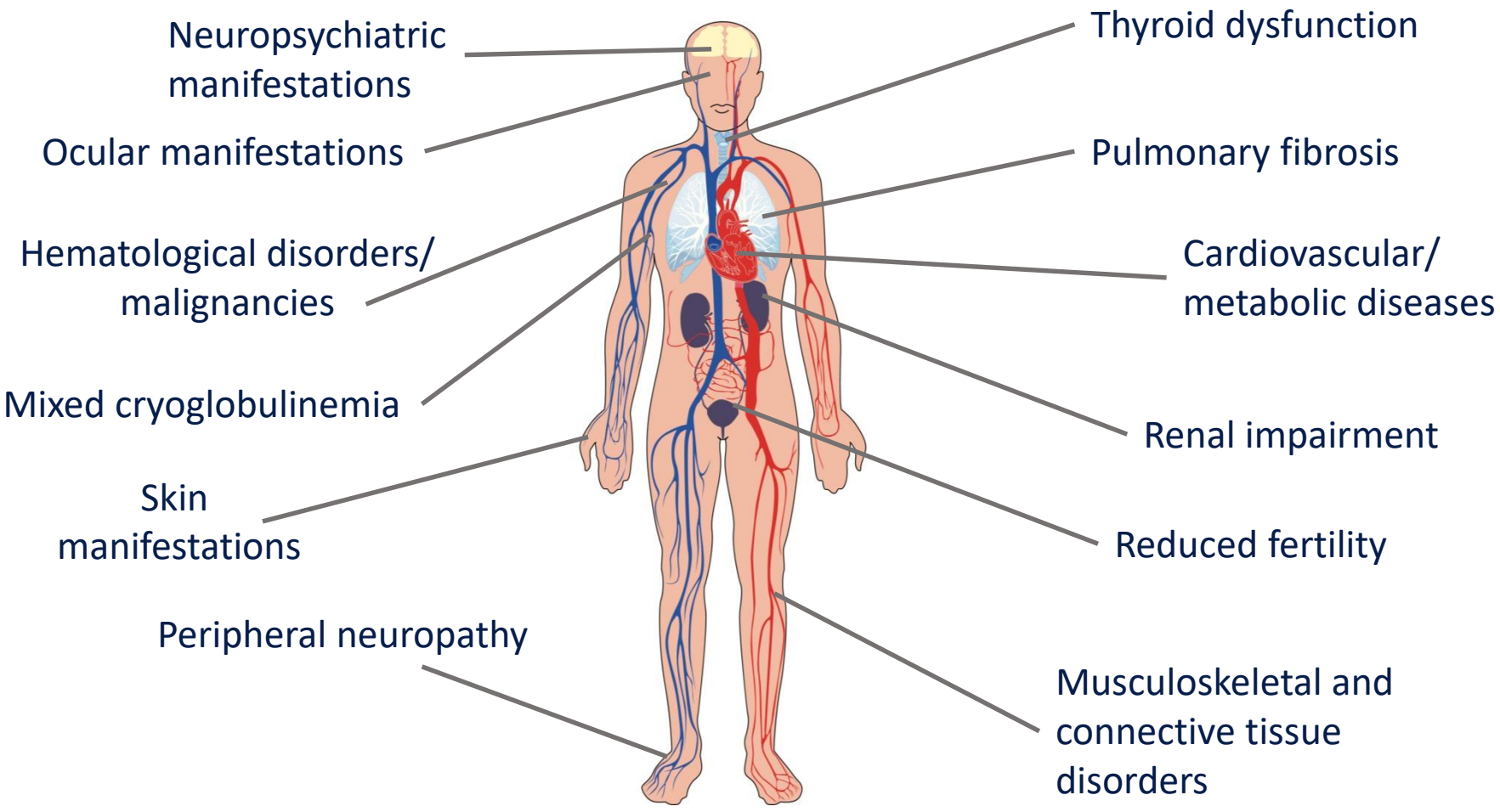
WHO. Global report on access to hepatitis C treatment – focus on overcoming barriers. Available at: http://www.who.int/hepatitis/publications/hep-c-access-report/en/ (Accessed February 2017);
Image taken from Gower J, et al. J Hepatol 2014;61:S45–57

HCV Disease Progression



Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 2014; 21 Suppl 1: 34-59.

Extrahepatic Manifestations of Chronic HCV Infection

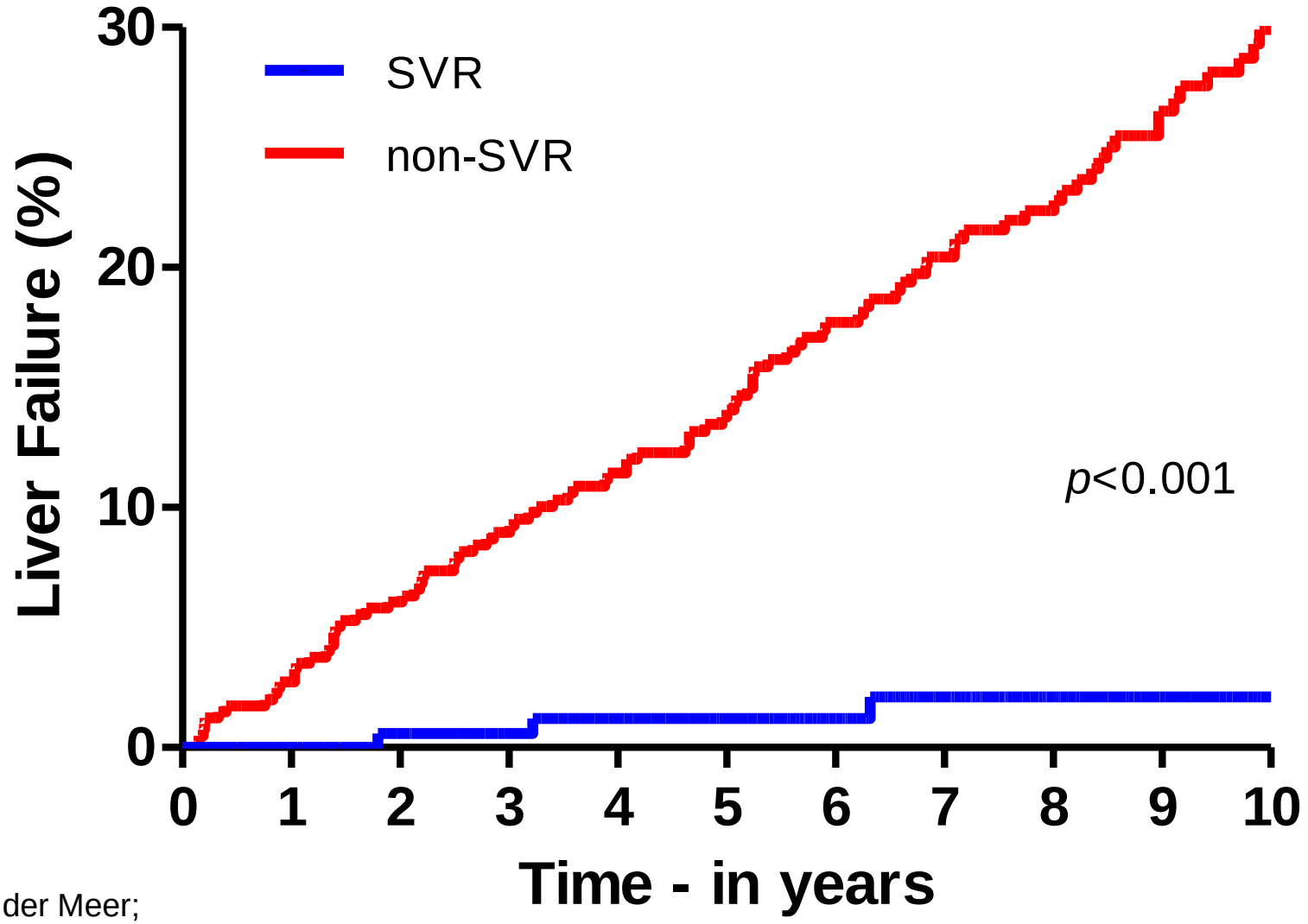


Extrahepatic disease can be present in up to **74%** of individuals with chronic HCV

Cacoub P, *et al. Dig Liver Dis* 2014; **46**(Suppl 5)**:**S165–S173; Negro F, *et al. Gastroenterology* 2015; **149:**1345–1360; Englert Y, *et al. Fertil Steril* 2007; **88:**607–11.

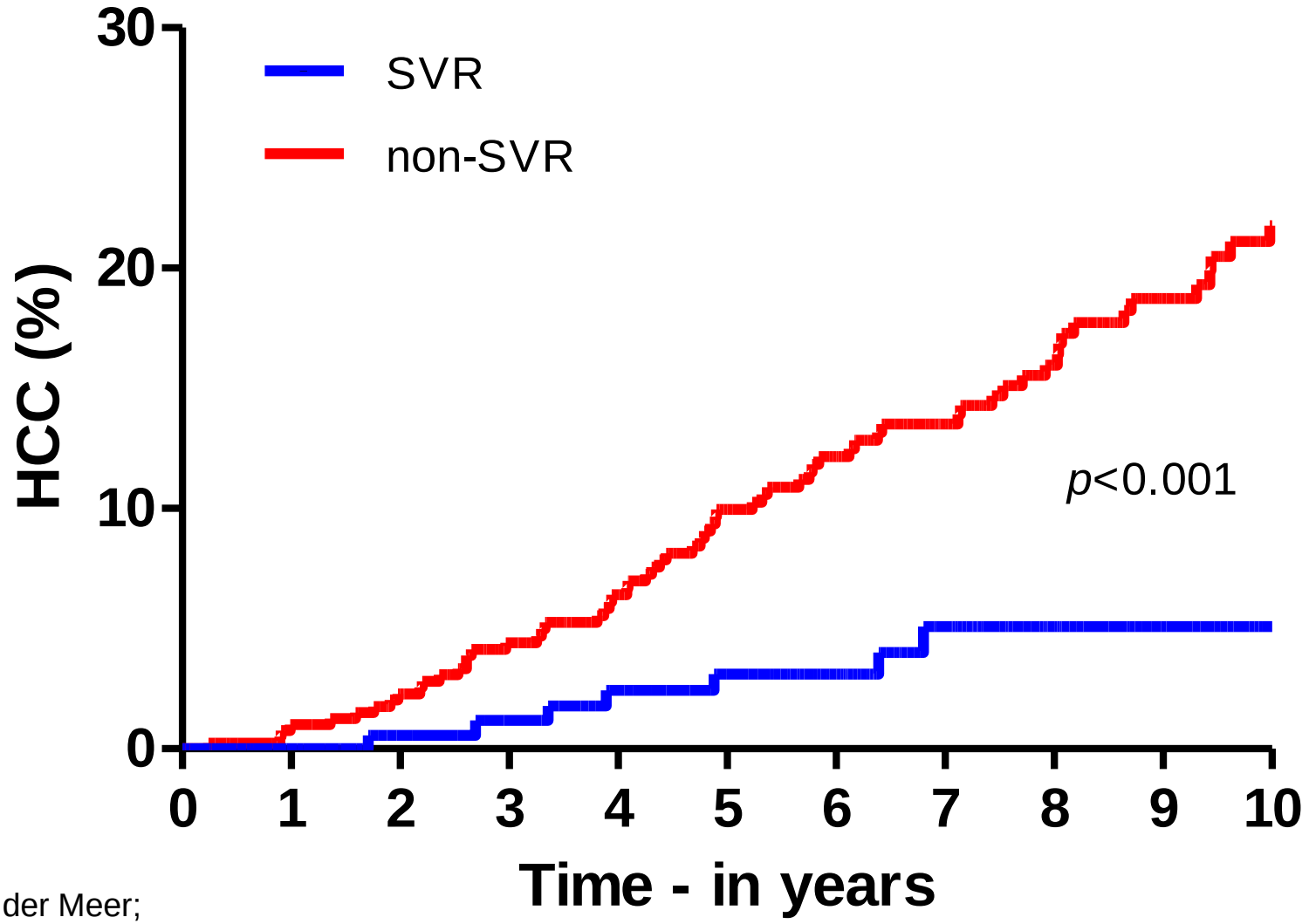
Impact of SVR on the Course of the Disease

SVR and Mortality Among Patients With Chronic Hepatitis C and Advanced Fibrosis



A.J. van der Meer;
JAMA 2012;308:2584-2593

SVR and Mortality Among Patients With Chronic Hepatitis C and Advanced Fibrosis

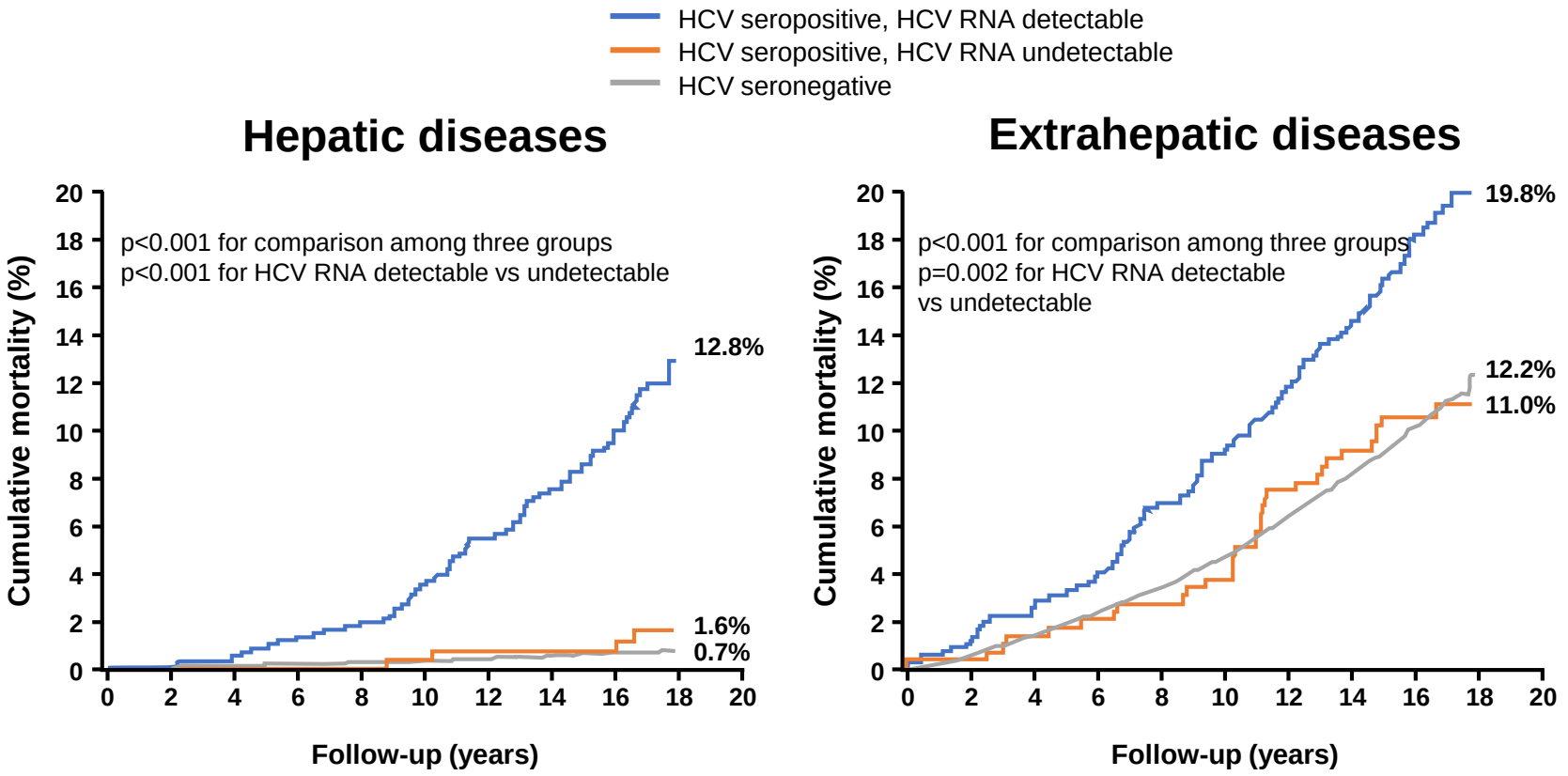


A.J. van der Meer;
JAMA 2012;308:2584-2593

HCV Cure Decreases Mortality from Both Hepatic and Non-hepatic Diseases

23,820 adults in Taiwan; 1095 anti-HCV positive,

69.4% with detectable HCV RNA

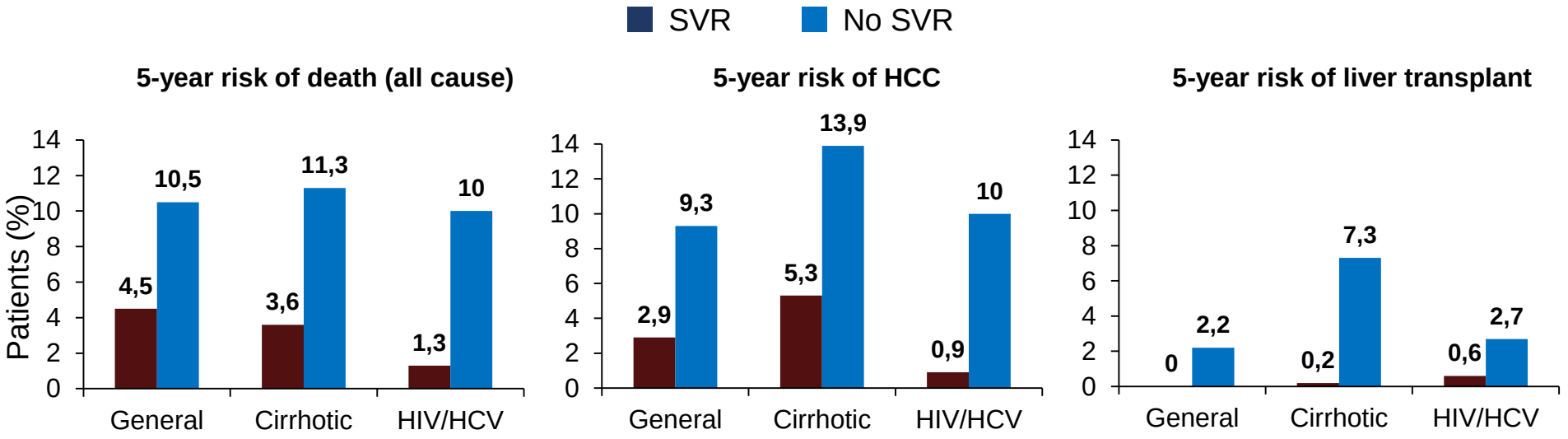


- Lee MH, et al. J Infect Dis 2012;206:469–77

SVR is associated with a reduced mortality, HCC and transplant

Meta-analysis of 129 studies of IFN-based therapy in 34,563 HCV patients

- Achieving SVR was associated with:
  - **62–84%** reduction in all-cause mortality
  - **68–79%** reduction in risk of HCC
  - **90%** reduction in risk of liver transplant



Saleem J, et al. AASLD 2014; Poster # 44

SVR – Patient-relevant End Point ?

- According to the German IQWiG Institute
  - SVR is surrogate end-point
  - SVR is not a validated patient-relevant end-point
  - After major critisms of scientific associations (DGVS, DGIM) at the G-BA: some non-quantifiable benefit, reduction of HCC risk possible

Limitations of Evidence-based Medicine

Objectives: To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design: Systematic review of randomised controlled trials.
Both authors without any COI.
The study not funded by industry.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Smith GC, Pell JP., BMJ 2003;327(7429):1459-61

Limitations of Evidence-based Medicine

Main outcome measure:
Death or major trauma.

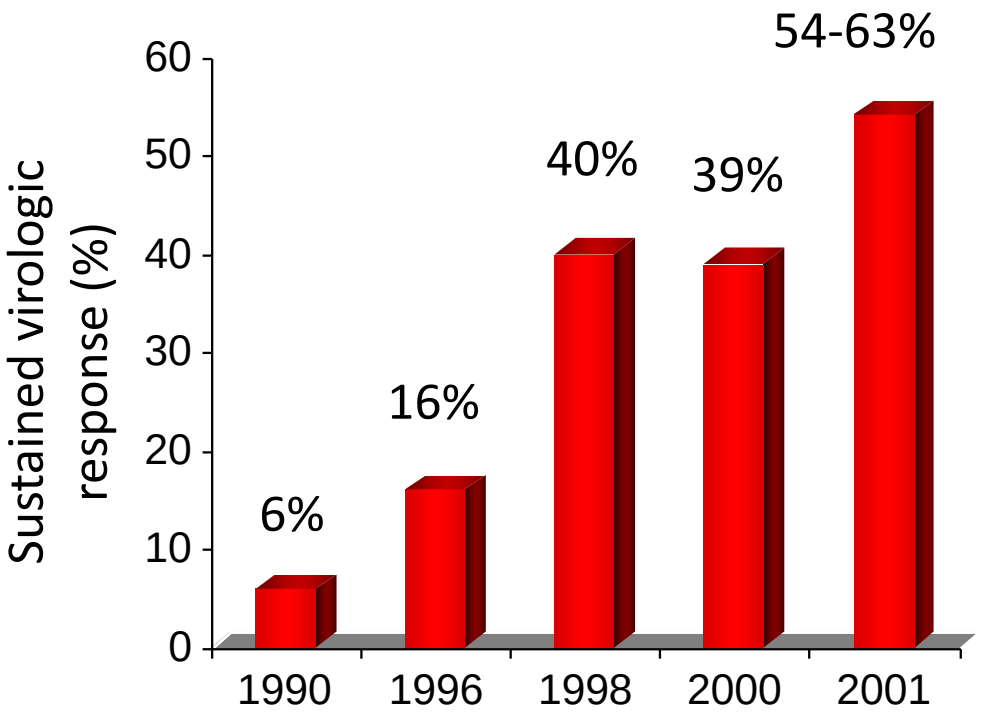
Results: We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions: As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Smith GC, Pell JP., BMJ 2003;327(7429):1459-61

Treatment of Hepatitis C

Treatment of chronic hepatitis C



´90 IFNa 3x3 MU x 24 wks
Davis et al., NEJM 1989

´96 IFNa 3x3 MU x 48 wks
Poynard et al., NEJM 1995
Poynard et al., Hepatology 1996

´98 IFNa + Ribavirin
McHutchison et al., NEJM 1998
Poynard et al., Lancet 1998

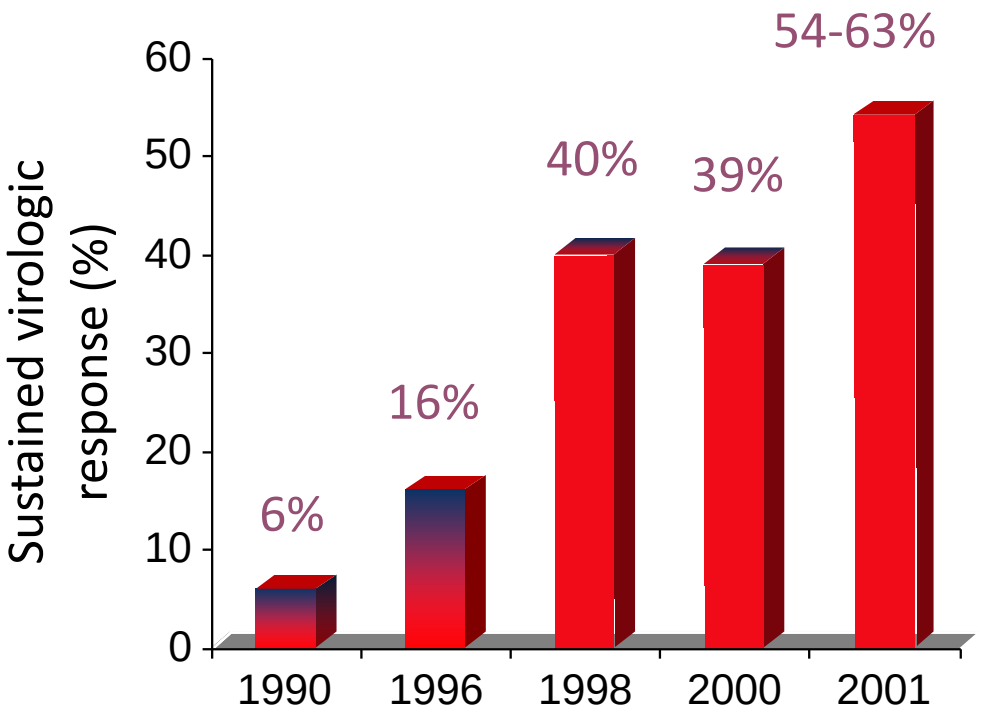
´00 PEG-IFNa2a
Zeuzem et al., NEJM 2000

´01 PEG-IFNa2b + RBV
Manns et al., Lancet 2001

´01 PEG-IFNa2a + RBV
Fried et al., NEJM 2002

´02 PEG-IFNa2a + RBV
Hadzyannis et al., Ann Intern Med 2004

Treatment of chronic hepatitis C



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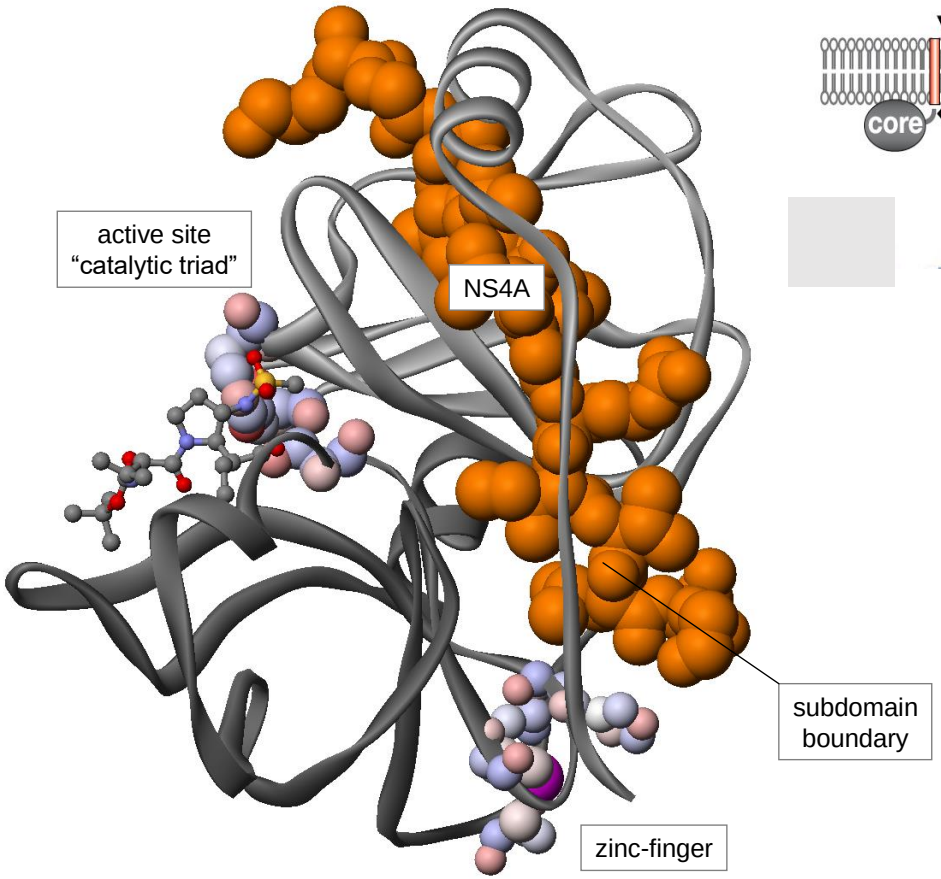
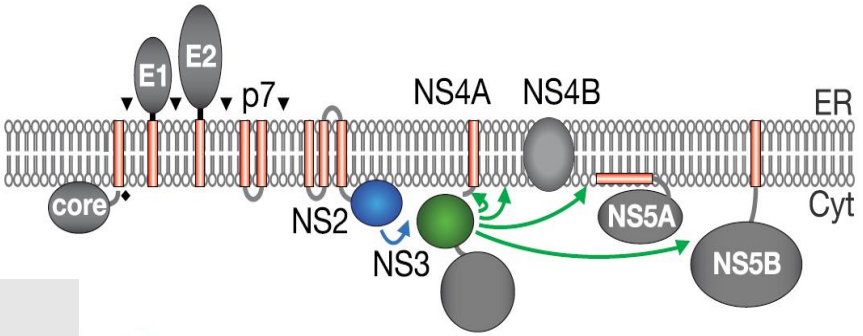
Hadzyannis et al., Ann Intern Med 2004

NS3 protease structure and function

Structure and function





STRUCTURE and FUNCTION

- **NS3 protease domain (aa 1-181)**
- **serine protease**
- **chymotrypsine-like fold**
  - polyprotein processing
- **active site “catalytic triad” (His57, Asp81, Ser139)**
- **oxyanion hole (Gly137)**
- **zinc-finger (Cys97, Cys99, Cys145)**
- **NS4A is a cofactor that directs the localization of NS3 and modulates its enzymatic activities**

Lorenz et al., *Nature* 2006
Kronenberger et al., *Clin Liver Dis* 2008
Shimakami et al. *Gastroenterology* 2011

Virologic response rates in treatment naive patients (no head-to-head data)

	ADVANCE (TVR)		SPRINT-2 (BOC)	
	PR + TVR	PR	PR + BOC	PR
RVR (wk 4)	66-68%	9%	-	-
Wk 8 (LI + 4 wk)	-	-	Not reported	Not reported
eEVR[1]	57-58%	8%	44%	N/A
EoT	81-87%	63%	71-76%	53%
Relapse	9%	28%	9%	22%
SVR (all)	69-75%	44%	63-66%	38%

RVR, rapid virologic response; LI, lead-in; eRVR, extended RVR;
EoT, end of treatment; SVR, sustained virologic response

[1] Different definitions of eEVR in ADVANCE and SPRINT-2

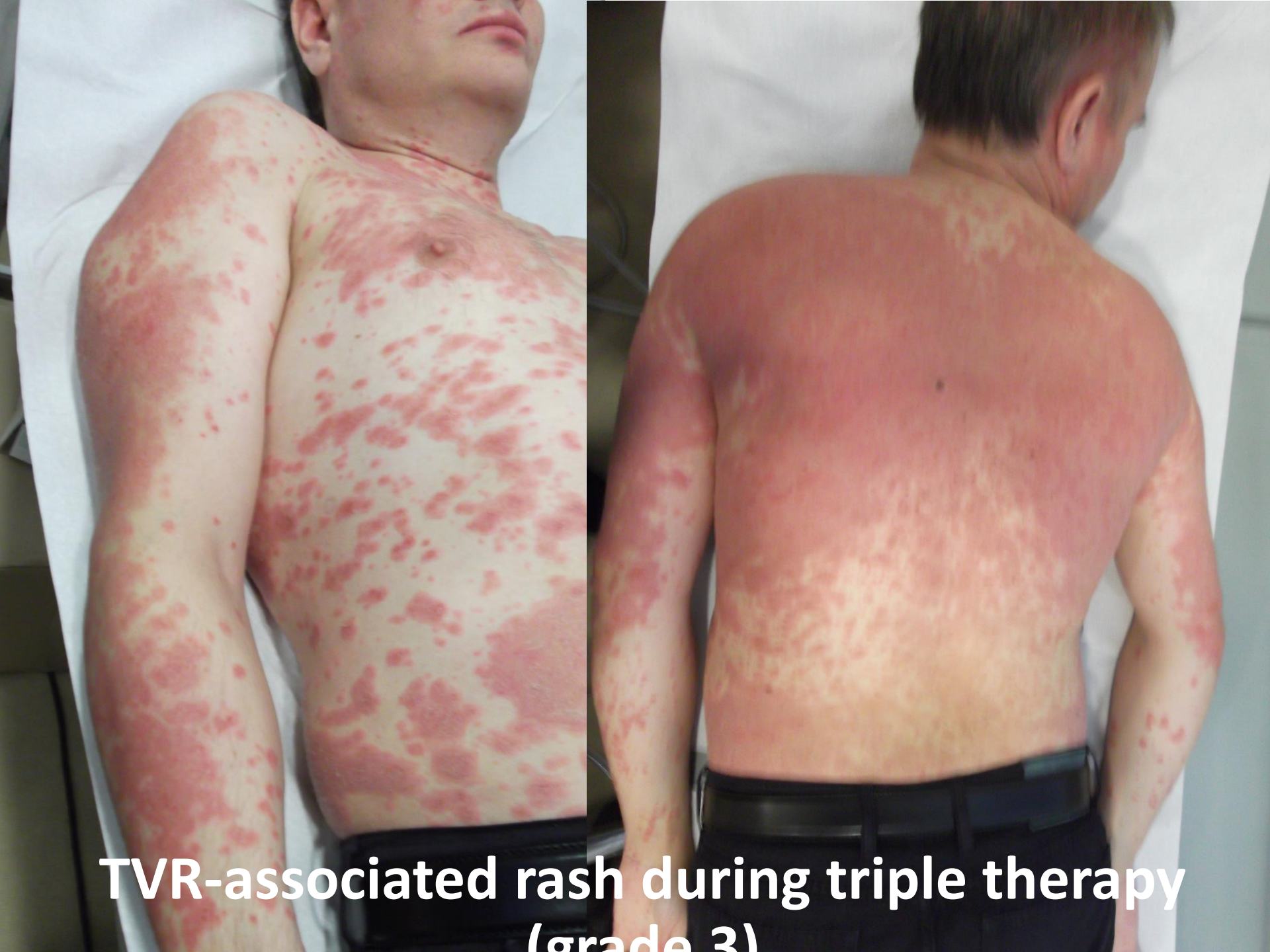
Jacobson et al., NEJM 2011
Reddy et al., APASL 2011
Poordad et al., NEJM 2011

Telaprevir and Boceprevir - Safety

(no head-to-head data)

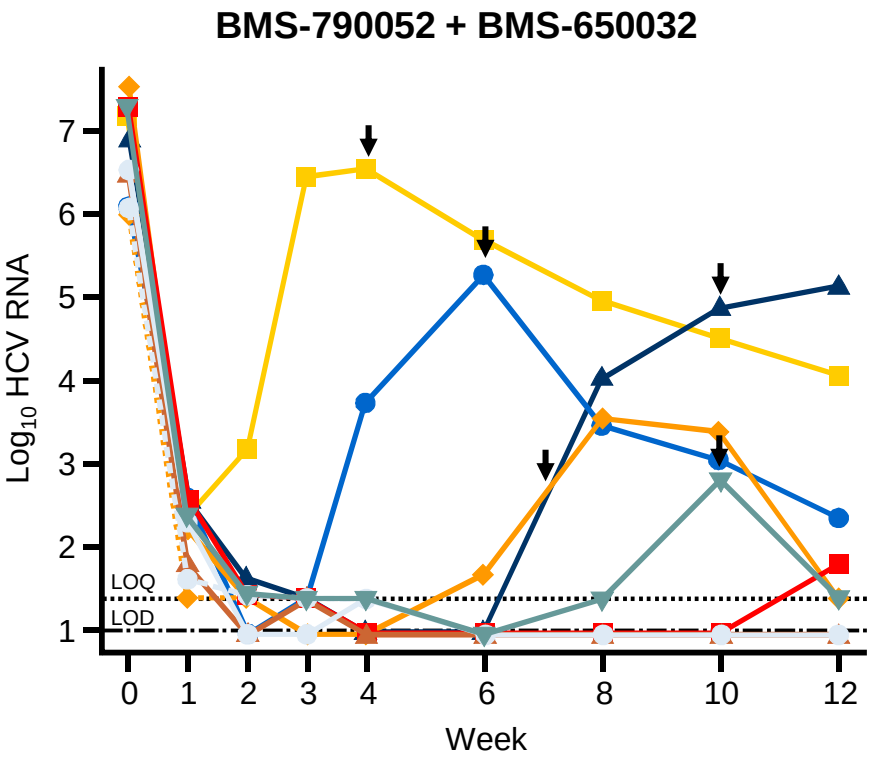
	ADVANCE (TVR)		SPRINT-2 (BOC)	
	TVR12/PR	PR	BOC RGT	PR
Discontinuation due to AEs	10%	7%	12%	16%
Discontinuation due to rash	7%	1%		
Anemia (<10 / < 8.5 g/dL)	36% / 9%	14% / 2%	45% / 5%	26% / 4%
Use of EPO	Not permitted		43%	24%

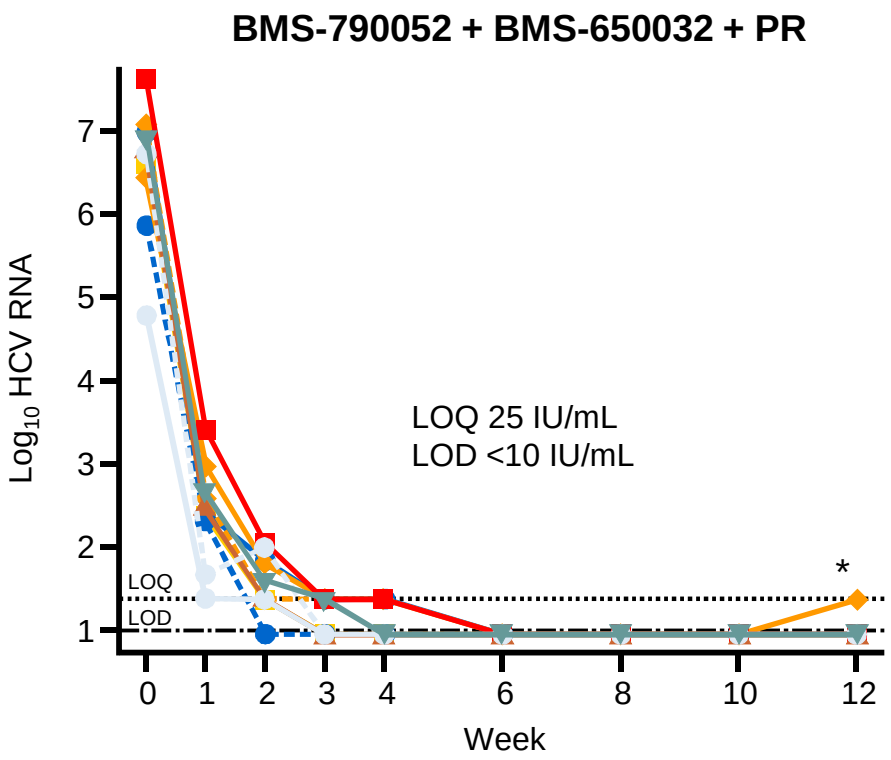
Jacobson et al., NEJM 2011
Poordad et al., NEJM 2011



TVR-associated rash during triple therapy (grade 3)

Pilot study with all oral anti-HCV treatment





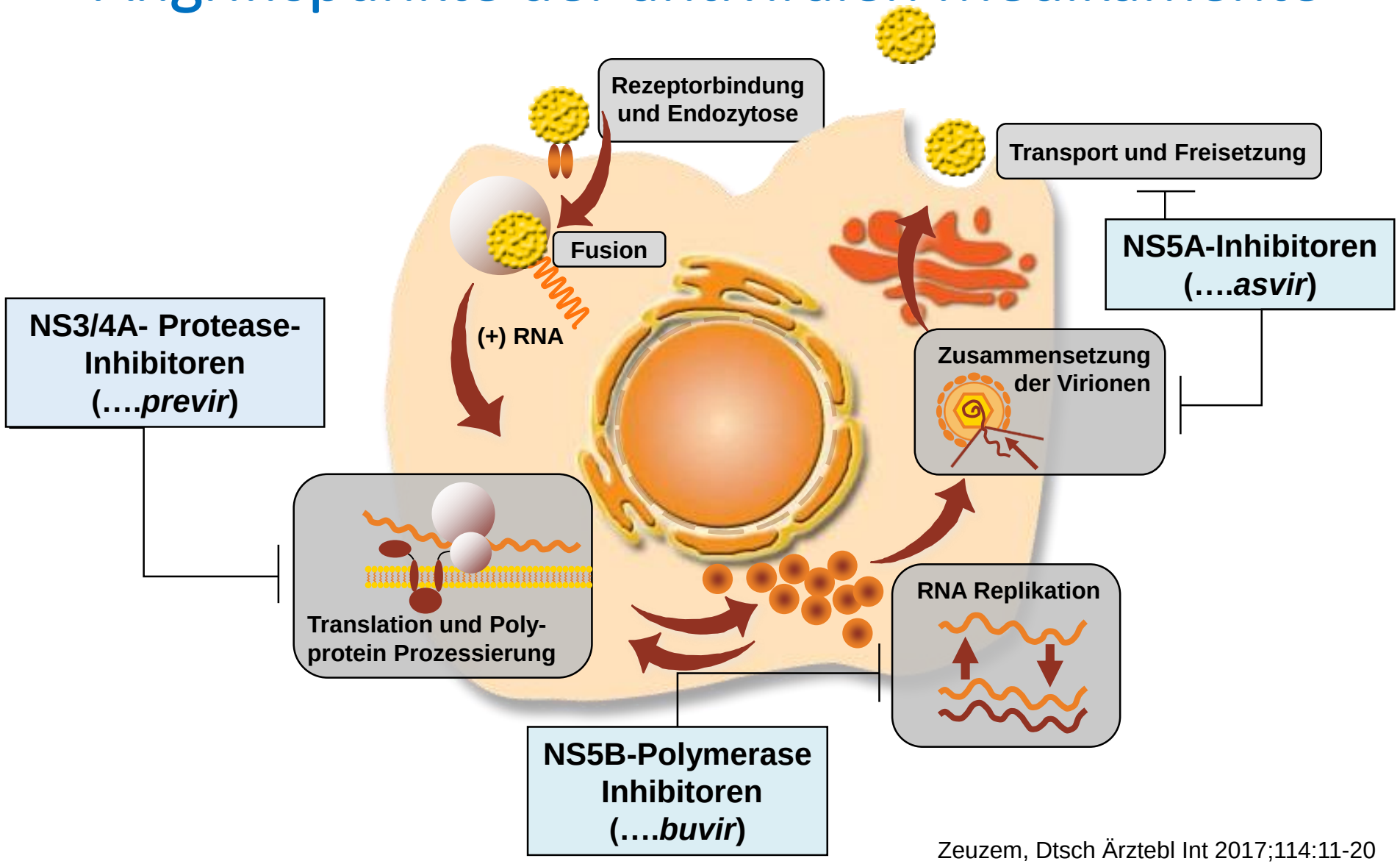
⬇ initiation of Peg-IFN/RBV

Lok A, et al. Hepatology 2010;52(Suppl.):877A
Lok A, et al. J Hepatol 2011;54(Suppl. 1):S536
Lok AS, et al., N Engl J Med. 2012;366(3):216-24

All-oral Hepatitis C Therapy: a Fast and Competitive Race

Zeuzem S., Nat Rev Gastroenterol Hepatol. 2014;11:644-5.

Replikationszyklus des Hepatitis C Virus und Angriffspunkte der antiviralen Medikamente



Zeuzem, Dtsch Ärztebl Int 2017;114:11-20

Genotypische antivirale Aktivität

	HCV-1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6
Sofosbuvir + Ledipasvir	x			x	x	x
Sofosbuvir + Velpatasvir	x	x	x	x	x	x
Grazoprevir + Elbasvir	x			x		(x)
Glecaprevir + Pibrentasvir	x	x	x	x	x	x

Wirksamkeit und Verträglichkeit dualer antiviraler Kombinationen

	SVR	Nebenwirkungen	Laborwert-veränderungen
Sofosbuvir + Ledipasvir	> 95%	Kopfschmerzen, Erschöpfung	Amylase, CK
Sofosbuvir + Velpatasvir	> 95%	Kopfschmerzen, Erschöpfung, Übelkeit	Amylase, CK
Grazoprevir + Elbasvir	> 95%	Verminderter Appetit, Schlaflosigkeit, Angst, Depression, Schwindel, Kopfschmerzen, Übelkeit, Diarrhö, u.a., Pruritus, Arthralgie, Ermüdung, Asthenie, Reizbarkeit	Bilirubin, GPT
Glecaprevir + Pibrentasvir	> 95%	Kopfschmerzen, Durchfall, Übelkeit, Fatigue	Bilirubin, GPT

Wichtige Medikamenteninteraktionen* (DDI) dualer antiviraler Kombinationen

	DDI
Sofosbuvir + Ledipasvir	Amiodaron, Antikonvulsiva, Antacida, PPI (hohe Dosis), Rifampicin, Johanniskraut, Statine
Sofosbuvir + Velpatasvir	Amiodaron, Antikonvulsiva, Antacida, PPI (hohe Dosis), Rifampicin, Efavirenz, Johanniskraut, Statine
Grazoprevir + Elbasvir	Dabigatran, Antikonvulsiva, Antimykotika, Bosentan, Johannniskraut, Atazanavir, Darunavir, Lopinavir, u.a., Efavirenz, Statine, Ciclosporin, Modafinil
Glecaprevir + Pibrentasvir	Dabigatran, Antikonvulsiva, Rifampicin, Ethinylestradiol, Johanniskraut, Atazanavir, Darunavir, Efavirenz, Statine, Ciclosporin, Omeprazol

*HEP Drug Interactions, University of Liverpool: http://www.hep-druginteractions.org
*HEP Mobile Apps (Apple, Android)

Posologie dualer antiviraler Kombinationen

	Dosis pro Tablette	Tablettenzahl	Nahrungseffekt
Sofosbuvir + Ledipasvir	400 mg / 90 mg	1 Tablette / Tag	mit oder ohne
Sofosbuvir + Velpatasvir	400 mg / 100 mg	1 Tablette / Tag	mit oder ohne
Grazoprevir + Elbasvir	100 mg / 50 mg	1 Tablette / Tag	mit oder ohne
Glecaprevir + Pibrentasvir	100 mg / 40 mg	3 Tabletten / Tag	mit Nahrung

Charakteristika dualer antiviraler Kombinationen

	Genotypische Aktivität	CKD-4,5	decompensierte Zirrhose
Sofosbuvir + Ledipasvir	nicht GT-2 & GT-3	Nein	Ja
Sofosbuvir + Velpatasvir	pangenotypisch	Nein	Ja
Grazoprevir + Elbasvir	nur GT-1 & GT-4	Ja	Nein
Glecaprevir + Pibrentasvir	pangenotypisch	Ja	Nein

Profil: Sofosbuvir + Velpatasvir (Epclusa®)

Empfohlene Behandlung und Dauer für alle HCV-Genotypen

Patientengruppe[a]	Behandlung und Dauer
Patienten ohne Zirrhose und Patienten mit kompensierter Zirrhose	Epclusa für 12 Wochen Die Zugabe von Ribavirin kann bei Patienten mit einer Infektion vom Genotyp 3 und kompensierter Zirrhose erwogen werden
Patienten mit dekompensierter Zirrhose	Epclusa + Ribavirin[b] für 12 Wochen

[a] Einschließlich Patienten mit Koinfektion mit HIV und Patienten mit rezidivierender HCV-Infektion nach Lebertransplantation

[b] RBV 1000-1200 mg/Tag bei CPT B vor LTx;
RBV 600 mg/Tag bei CPT C vor LTx und CPT B oder C nach LTx

Fachinformation Epclusa, September 2019

Profil: Glecaprevir + Pibrentasvir (Maviret®)

(1) Empfohlene Behandlungsdauer für Maviret bei therapienaiven Patienten

Genotyp	Empfohlene Behandlungsdauer	
	Ohne Zirrhose	Mit Zirrhose
GT 1, 2, 4-6	8 Wochen	8 Wochen
GT 3	8 Wochen	12 Wochen

(2) Empfohlene Behandlungsdauer für Maviret bei Patienten, bei denen eine Vorbehandlung mit peg-IFN + Ribavirin +/- Sofosbuvir oder mit Sofosbuvir + Ribavirin versagt hat

Genotyp	Empfohlene Behandlungsdauer	
	Ohne Zirrhose	Mit Zirrhose
GT 1, 2, 4-6	8 Wochen	12 Wochen
GT 3	16 Wochen	16 Wochen

Fachinformation Maviret, September 2019

Vergleich der pan-genotypischen Kombinationen

Sofosbuvir + Velpatasvir

- ✓ Therapiedauer 12 Wochen
- ✓ Dekompensierte Zirrhose
- ✓ CrCl > 30 ml/min
- ✓ RBV bei GT3 Patienten mit Zirrhose und allen Patienten mit dekompensierter Zirrhose

Glecaprevir + Pibrentasvir

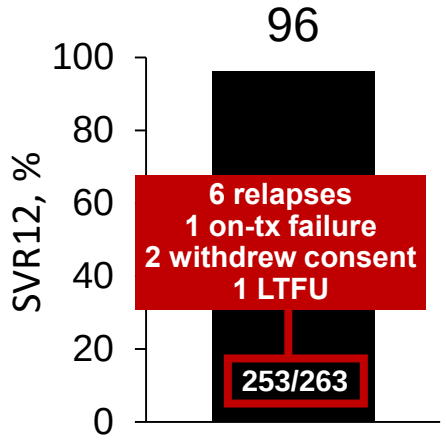
- ✓ Therapiedauer bei nicht-vorbehandelten Patienten 8 Wochen (12 Wo. bei GT3 mit Zirrhose)
- ✓ Behandlung auch bei Niereninsuffizienz möglich, nicht aber bei Patienten mit dekompensierter Zirrhose
- ✓ Therapiedauer bei vorbehandelten Patienten zwischen 8 Wo. (ohne Zirrhose), 12 Wo. (mit Zirrhose) und 16 Wochen (GT3 mit/ohne Zirrhose)
- ✓ Kein RBV bei GT3-Patienten mit Zirrhose

Spezielle klinische Konstellationen

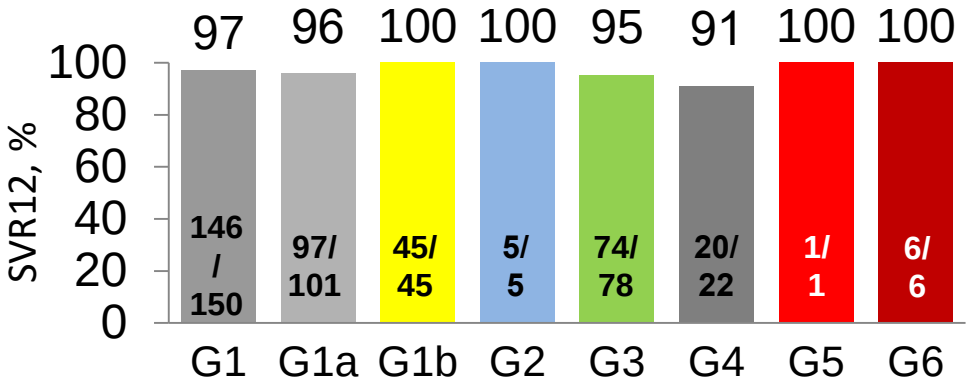
- Akute Hepatitis C
- Limitierte Studiendaten zu Kindern und Jugendlichen
- Zeitpunkt der antiviralen Therapie bei Patienten auf Transplantationslisten (“point-of-no-return”, Allokation HCV-positiver Organe)
- Zeitpunkt einer antiviralen Therapie bei Patienten mit chronischer Hepatitis C und einem in kurativer Intention behandelten HCC
- Therapie einer Hepatitis C bei Patienten mit einem nicht kurativ behandelbaren HCC
- Tripeltherapien für Patienten mit virologischem Relapse nach DAA Therapie

SOF/VEL/VOX for 12 weeks as a salvage regimen in NS5A inhibitor-experienced G1–6 patients

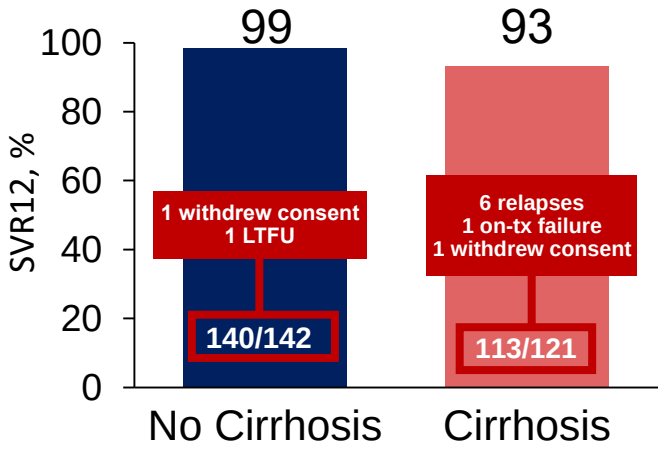
(i) Overall SVR12 (ITT)



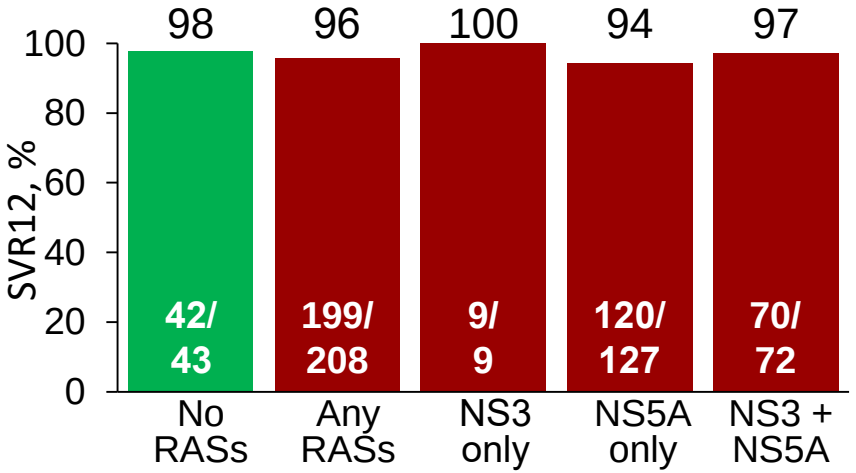
(ii) SVR by genotype



(iii) SVR by cirrhosis

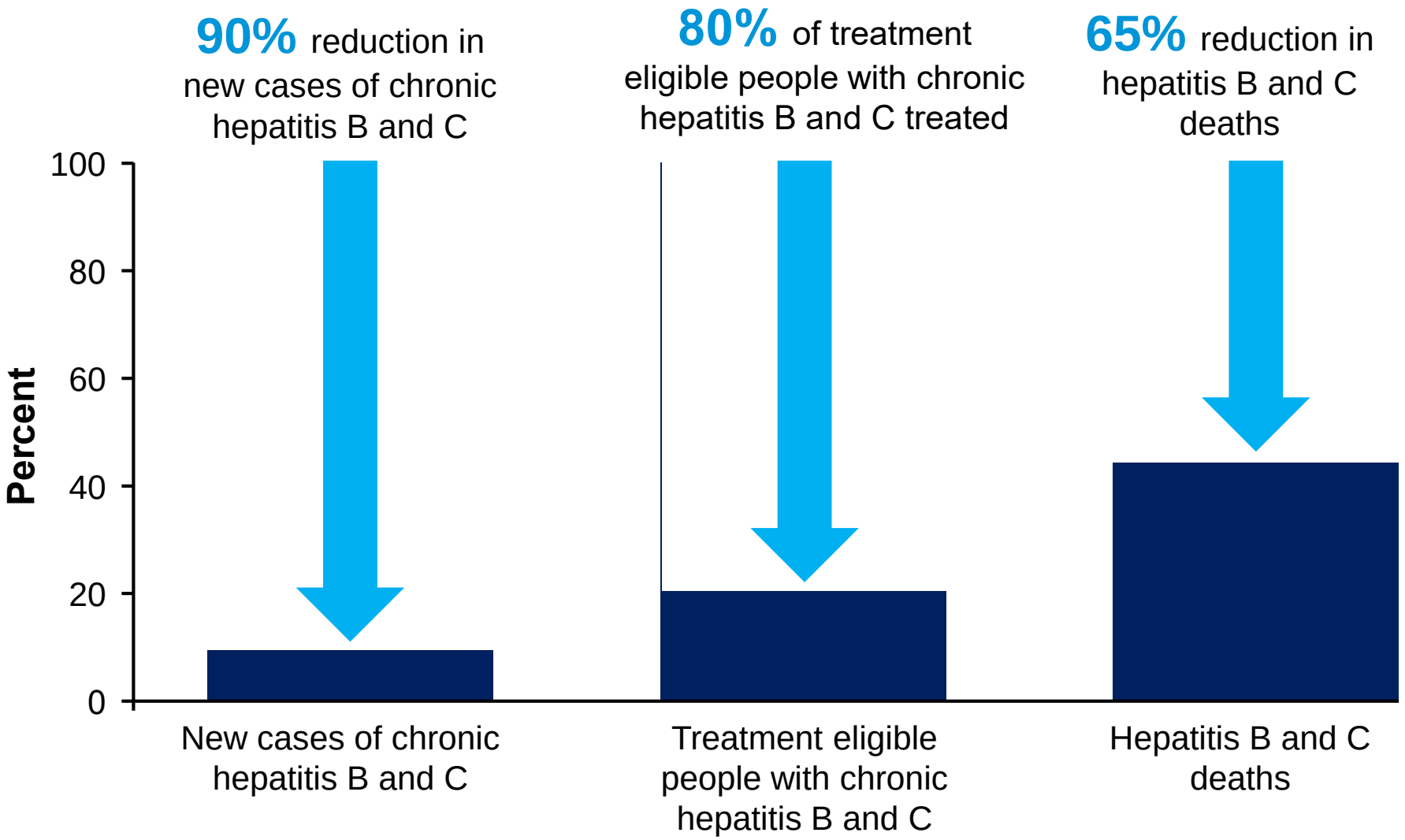


(iv) SVR by NS5A RASs



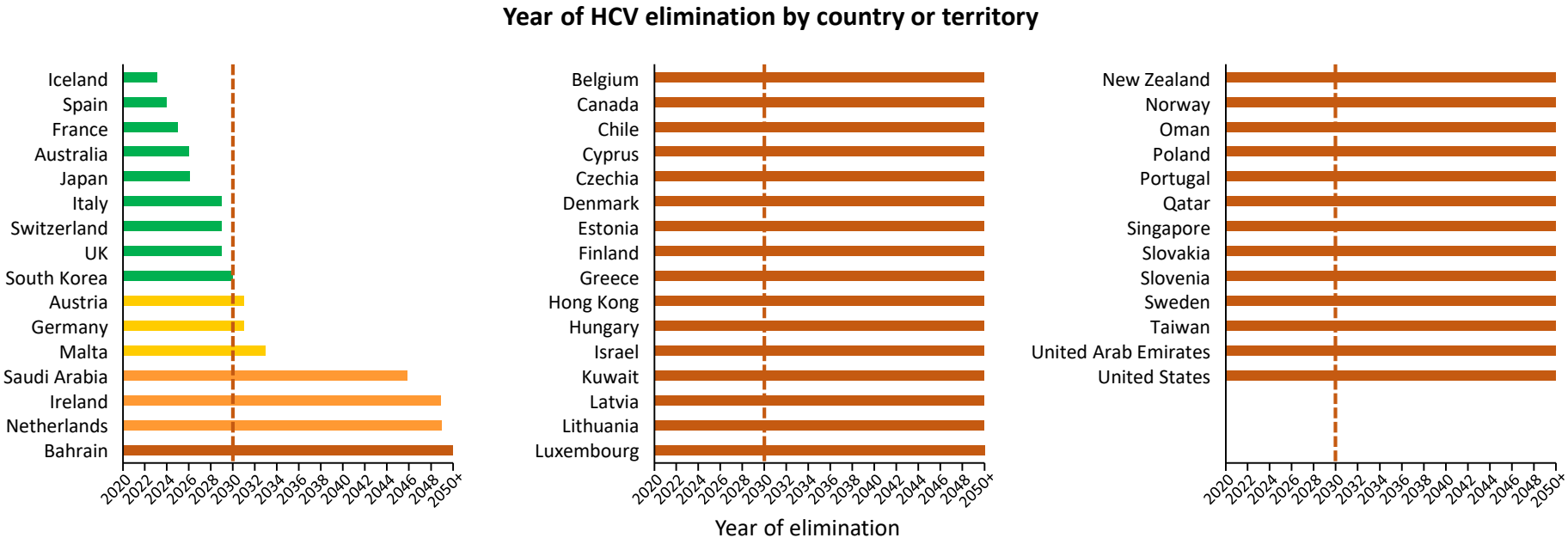
Bourlière M, et al., NEJM 2017

Global targets achieved if viral hepatitis is controlled by 2030



World Health Organization. Draft global health sector strategies. Viral Hepatitis, 2016–2021. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1 (accessed September 2016)

Global timing of hepatitis C virus elimination: Estimating the year countries will achieve the World Health Organization elimination targets



80% (36/45) of high-income countries/territories are not on track to meet the WHO 2030 HCV elimination targets

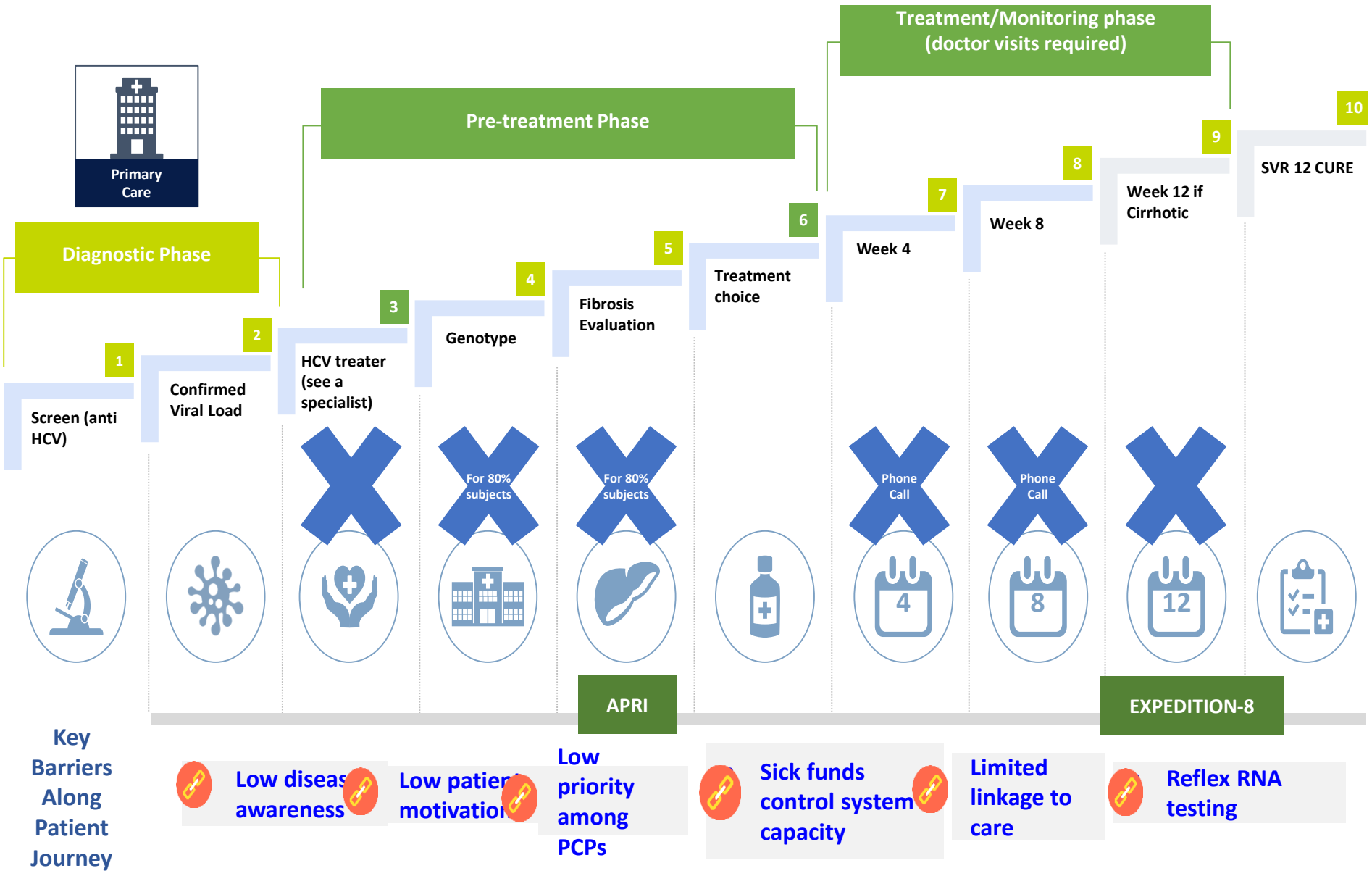
67% (30/45) are off-track by ≥20 years

Razavi H, et al. EASL 2019, Vienna, Austria. #SAT-260

Zusammenfassung

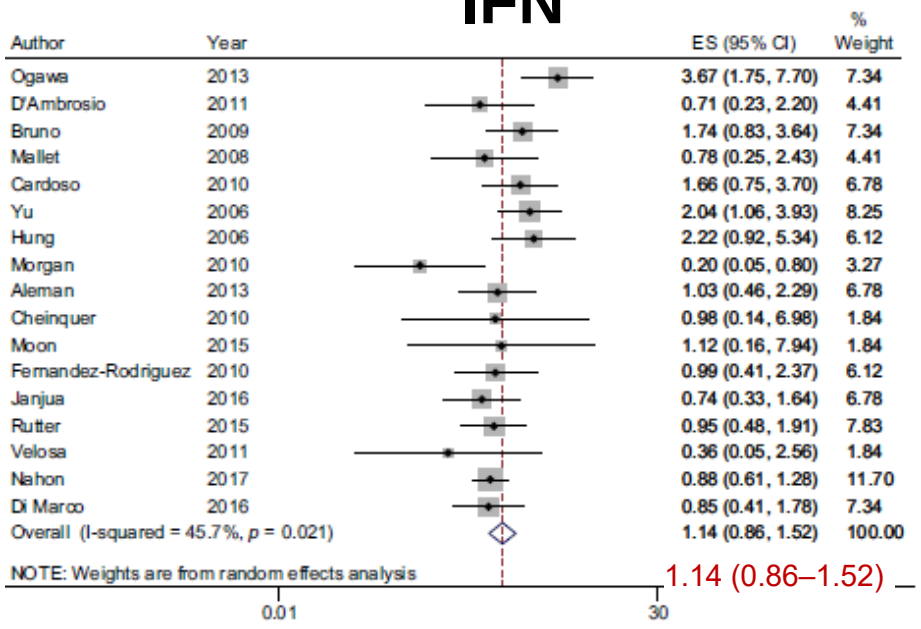
- Eine Therapieindikation besteht für alle Patienten mit Hepatitis C, Screening !
- SOF/VEL und GLE/PIB sind pan-genotypische Kombinationen
- Andere Kombinationen haben in Deutschland nur eine Bedeutung bei der Optimierung der Behandlungskosten
- Protease-Inhibitoren sind bei Patienten mit einer dekompensierten Zirrhose kontraindiziert
- SOF ist bei Patienten mit schwerer Niereninsuffizienz nicht zugelassen
- SOF/VEL/VOX zugelassen für DAA-Nonresponder
- WHO-Ziele werden in vielen Ländern nicht erreicht werden

Treatment cascade simplification from 10 to only 4 steps ?

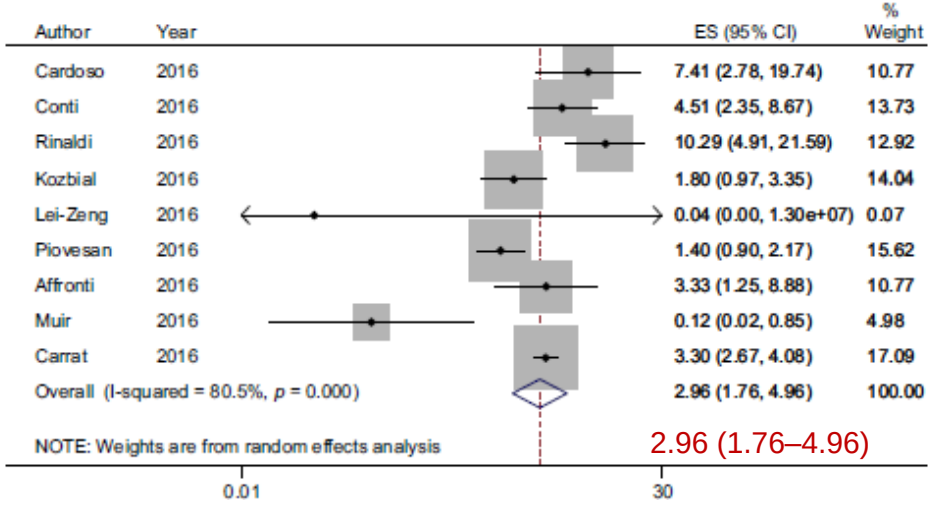


A meta-analysis of the risk of HCC occurrence following SVR to IFN or DAAs

IFN



DAA



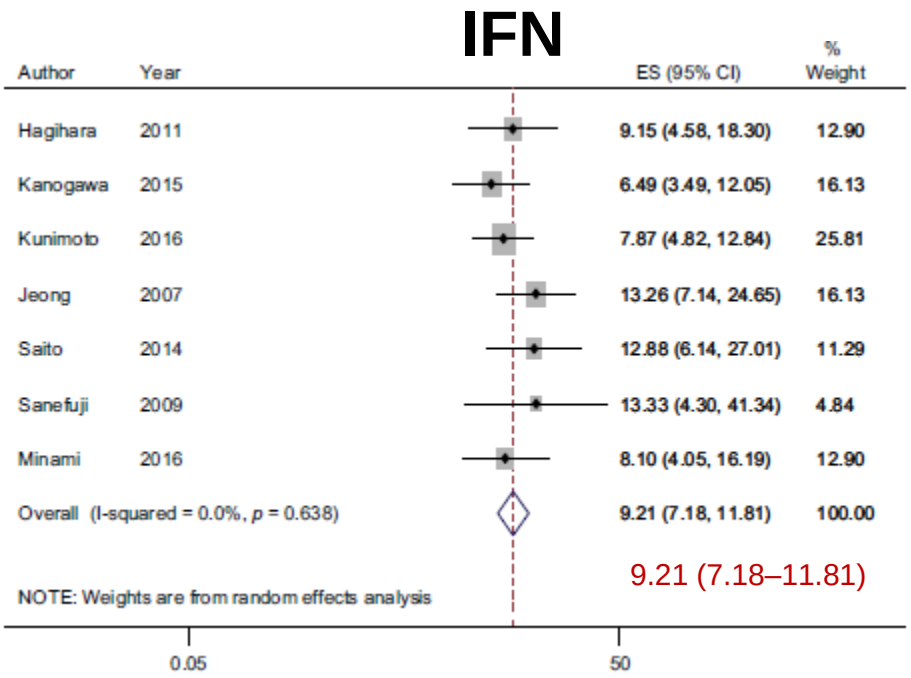
Meta regression of HCC occurrence

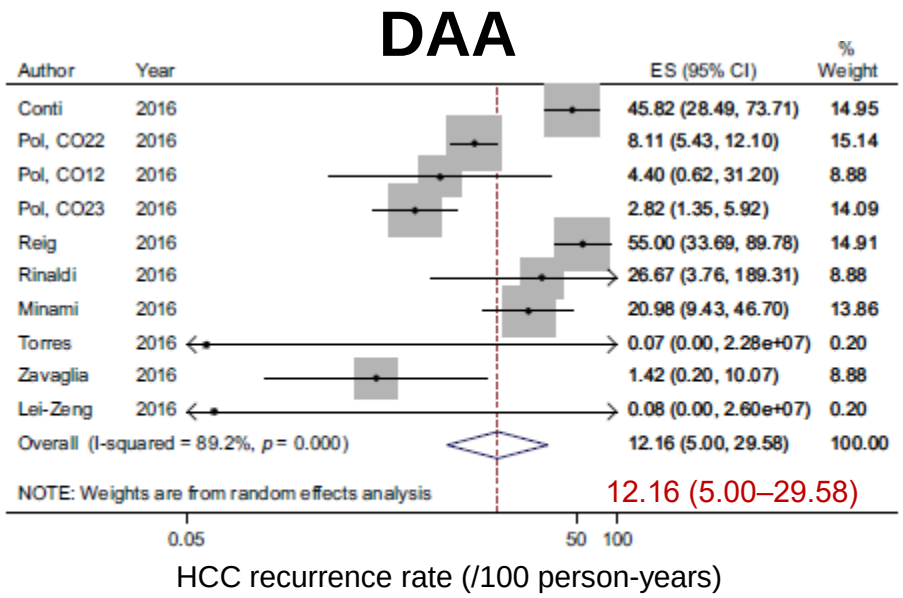
	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.88	0.75	0.56–0.99	0.04
Average age	1.11	1.06	0.99–1.14	0.12
DAA treatment	2.77	0.68	0.18–2.55	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12

RR: risk ratio

A meta-analysis of the risk of HCC recurrence following SVR to IFN or DAAs





Meta regression of HCC reccurrence

	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.86	0.79	0.55–1.15	0.19
Average age	1.11	1.11	0.96–1.27	0.14
DAA treatment	1.36	0.62	0.11–3.45	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12