Hepatitis C –
17 months experience
with Sofosbuvir/Ledipasvir (Harvoni)

Prof. Dr. Markus Cornberg
Klinik für Gastroenterologie, Hepatologie und Endokrinologie

Medizinische Hochschule
Hannover

Antalya, 13.05.2016

Markus Cornberg, Hannover Medical School

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Abbvie, BMS, Gilead, Janssen, Roche, Merck

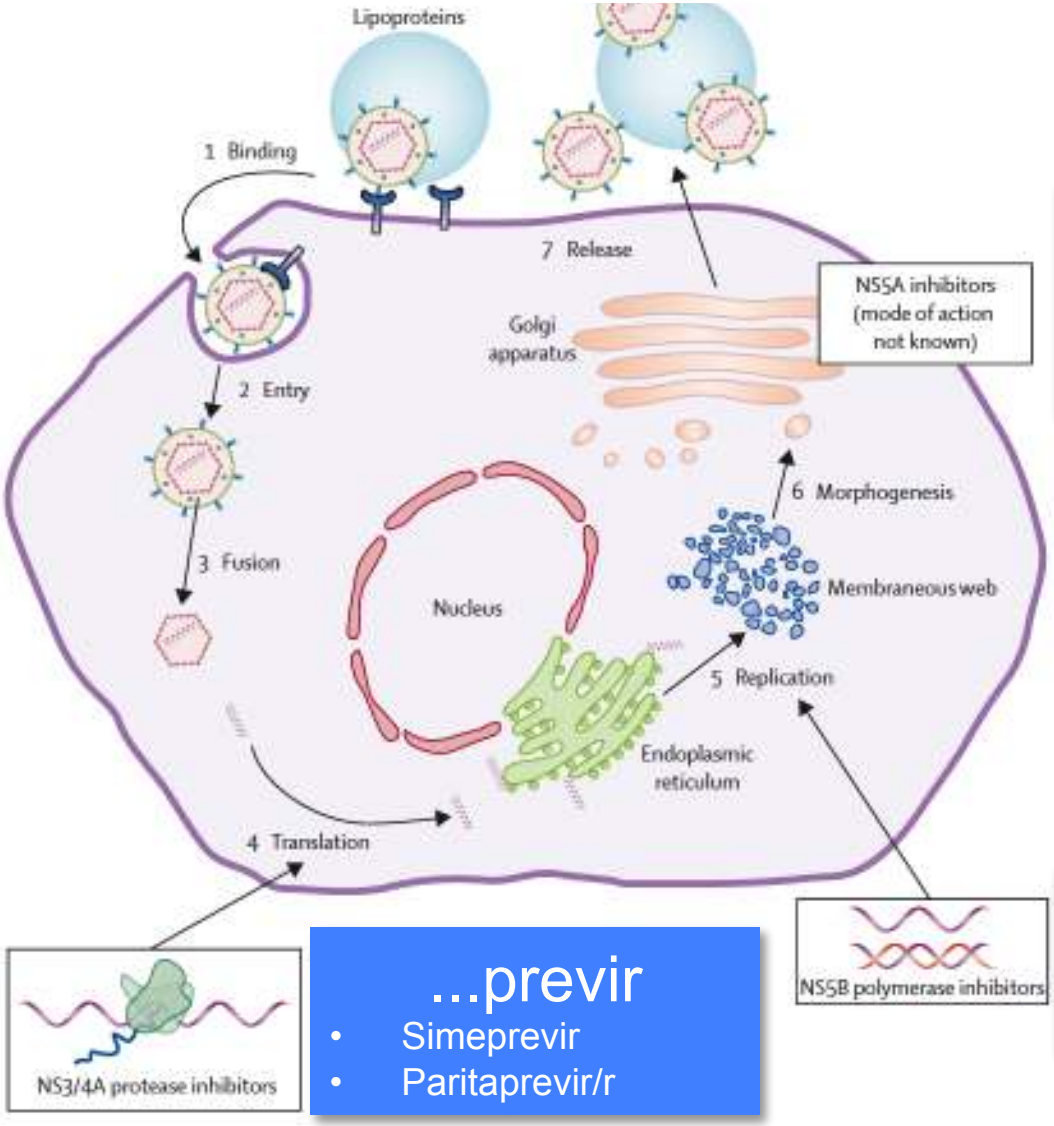
Disclaimer

- These non-promotional slides are intended to be used as educational material only in response to an unsolicited question or request

- Slides may contain information that is not within EMA or FDA approved product labeling and has not otherwise been approved by the EMA or FDA

- Information within this slide deck is related to investigational agents that are not approved by EMA or FDA and therefore the safety and efficacy have not yet been determined in humans

Available HCV DAA therapies 2016 (Germany)



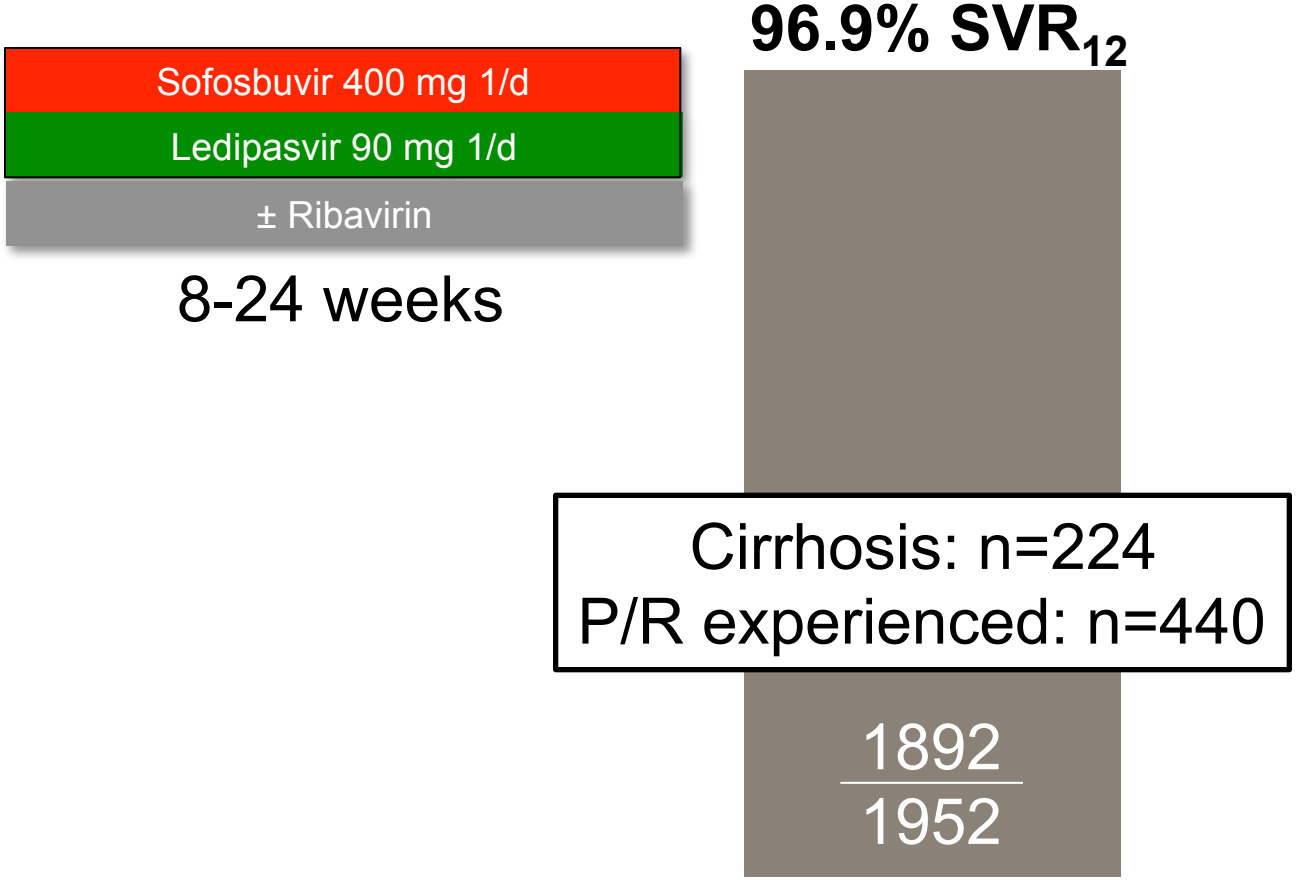
...asvir
- Daclatasvir
- Ledipasvir
- Ombitasvir

...buvir
- Sofosbuvir (NI)
- Dasabuvir (NNI)

...previr
- Simeprevir
- Paritaprevir/r

Adapted from Manns & Cornberg, Lancet Infectious Diseases 2013 May;13(5):378-9

Chronic Hepatitis C Genotype 1:
3x New England Journal of Medicine (April 2014)
Phase III ION-TRIALS

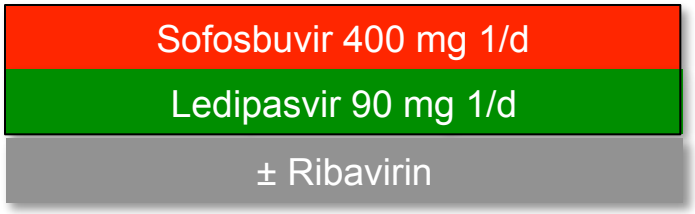


Questions:

1. Do we see similar SVR results for SOF/LDV in the real-world?
2. Is 8-week SOF/LDV treatment in naive patients without cirrhosis effective?
3. SOF/LDV: When to add Ribavirin or prolong to 24 weeks?
4. What is the clinical benefit of DAA treatment?
5. Safety in real-world situations?

Hannover Medical School
12/2014 - 5/2016

N=142 with SOF/LDV±RBV**



8-24 weeks

97.8% SVR_{12}

N=93 with FU12

90% F3/F4

2 patients with relapse
#1 Compliance issues
#2 CHILD B cirrhosis

plus n=30
Transplant Cohort
29/30 SVR (96.7%)*

*Ciesek et al., Transpl Infect Dis 2016.

**MHH, Data on file

REAL WORLD DATA 2016

US-Veterans

HCV-TARGET
Hepatitis C Therapeutic Registry and Research Network

Academic > Community
(also MHH, Germany)

Trio Health

Community > Academic

Named patient programs (CUP)
- France
- England
- Poland
- EU

DHC-R
Deutsches Hepatitis C-Register

250 German Centers

8 German Centers

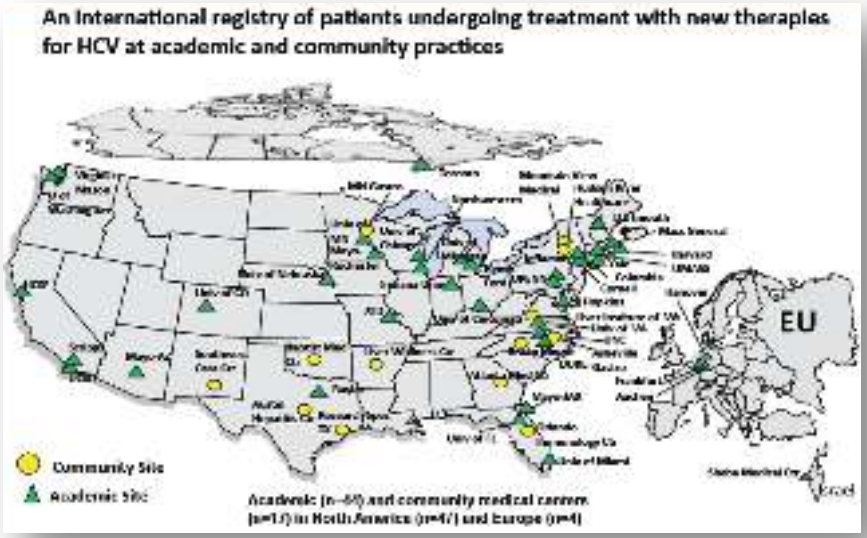
GECCO
GERMAN COHORT

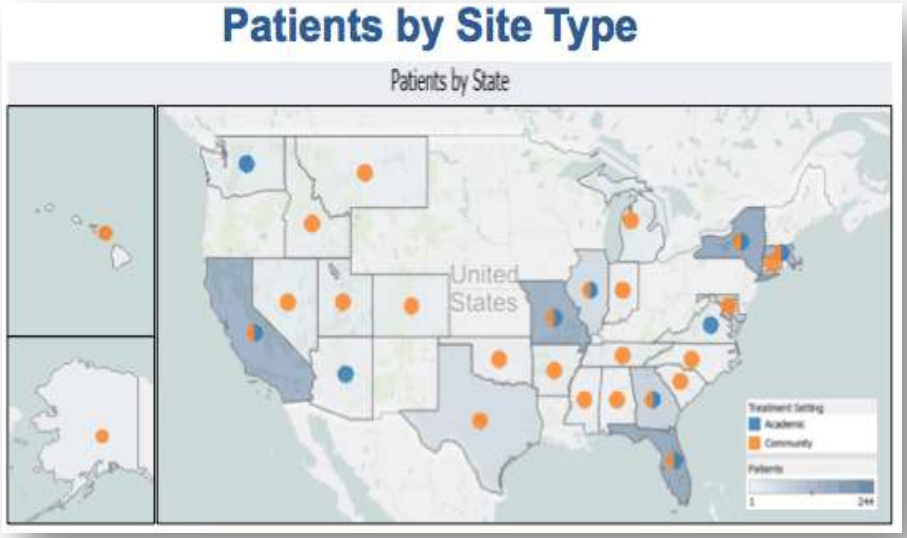
Single Center studies
MHH, IFI etc.

HEPA-C cohort

HCV-TARGET
Hepatitis C Therapeutic Registry and Research Network

Trio Health



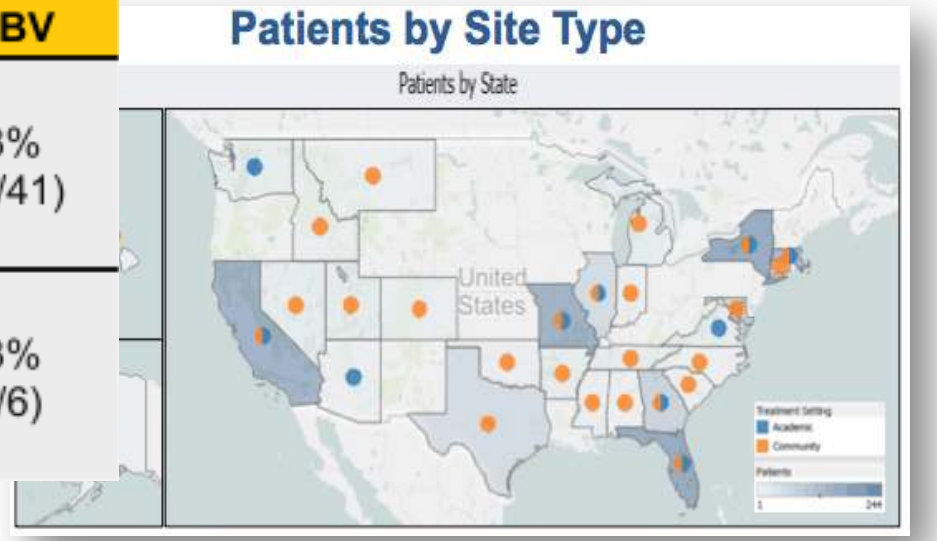


Different cohort may give different results

- Documentation / data quality (ITT versus PP analysis)
- Patients with advanced disease versus „easy to treat“ patients
- Treatment outside the recommendation (label)

	LDV/SOF ± RBV	SMV+SOF ± RBV	OBV/PTV/ RTV+ DSV ±RBV
SVR Within FDA Labeling	95% (1391/1462)	82% (27/33)	93% (38/41)
SVR Outside FDA Labeling	85% (115/135)	63% (5/8)	83% (5/6)

Trio Health



- Positive association with virologic failure (% distribution in the failure group vs the overall group)*:
  - Male (76% in failures vs 58% overall, *P*=0.008)
  - Cirrhosis (70% in failures vs 31% overall, *P*<0.001)
  - Platelets < 100,000/mL (40% in failures vs 11% overall, *P*<0.001)
  - Outside FDA labeling (as of March 2015; 33% in failures vs 10% overall, *P*<0.001)

*2-side asympt. p-value Pearson χ^2

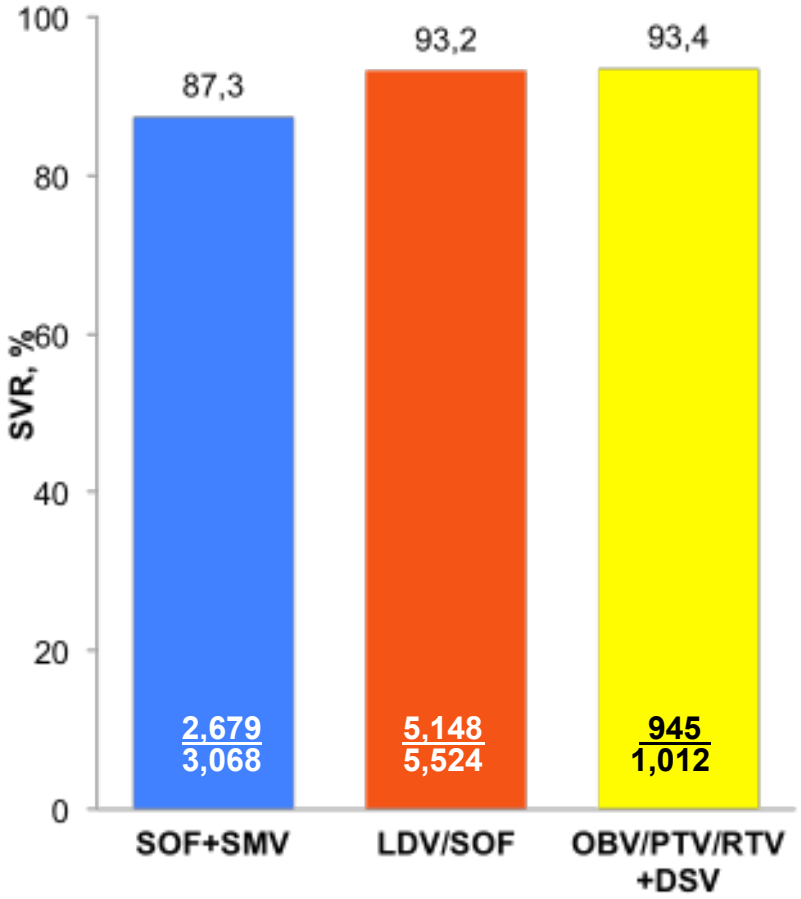
Afdhal, AASLD, 2015, LB-17

Real-World Effectiveness in 9,604 HCV patients treated with DAAs in the VA Cohort

Baseline Demographics

Patients	SOF+SMV* N=3,068	LDV/SOF N=5,524	OBV/PTV/ RTV+DSV N=1,012
Male, n (%)	2956 (96.3)	5320 (96.3)	976 (96.4)
GT1, n (%)	2363 (77.0)	4104 (74.3)	773 (76.4)
GT Other + unknown	705 (23.0)	1420 (25.7)	239 (23.6)
Cirrhosis, n (%)	2119 (69.1)	2121 (38.4)	350 (34.6)
Decompensated	1211 (39.5)	1091 (19.8)	129 (12.7)
HCC	345 (11.2)	278 (5.0)	21 (2.1)
Liver Transplant	248 (8.1)	176 (3.2)	2 (0.2)
HIV	120 (3.9)	270 (4.9)	18 (1.8)
Previous Tx – Boceprevir	177 (5.8)	450 (8.1)	17 (1.7)
Previous Tx - Telaprevir	67 (2.2)	95 (1.7)	0

SVR12



Data collected prior to September 2015
*SOF+SMV data were collected primarily in 2014 before other DAA approvals

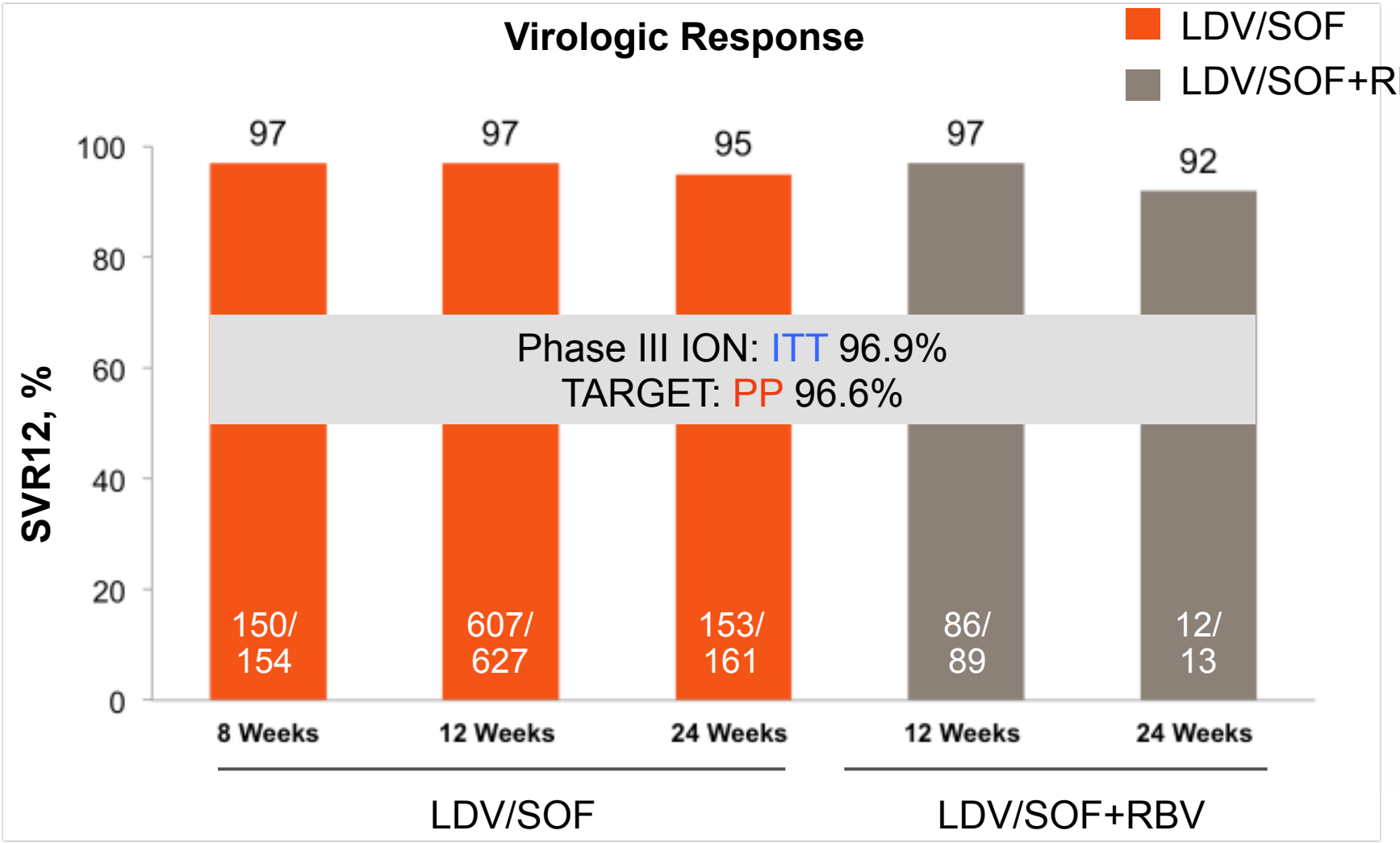
Treatment Outcomes with LDV/SOF±RBV for 8, 12, and 24 Weeks

Analysis of 1,270 patients who received LDV/SOF±RBV in HCV-TARGET, a multicenter, prospective, observational, real-world cohort study

	LDV/SOF N=1139	LDV/SOF+RBV N=131
Male, n (%)	647 (57)	90 (69)
Age, yr, median, range	60 (19-87)	61 (31-78)
Caucasian, n (%)	814 (72)	108 (82)
Black, n (%)	245 (22)	12 (9)
Treatment Status, n (%)		
Naïve	634 (56)	40 (31)
Experienced	505 (44)	91 (69)
DAA Experienced	143 (13)	24 (18)
Genotype, n (%)		
1a	751 (66)	79 (60)
1b	302 (27)	40 (31)
Cirrhosis, n (%)	396 (35)	83 (63)
Decompensated, n (%)	142 (13)	28 (21)
Liver transplant, n (%)	71 (6)	58 (44)
HIV, n (%)	35 (3)	4 (3)
Baseline PPI Use, n (%)	305 (27)	47 (36)

Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with LDV/SOF. Proton pump inhibitors should not be taken before LDV/SOF. (Harvoni® SmPC)

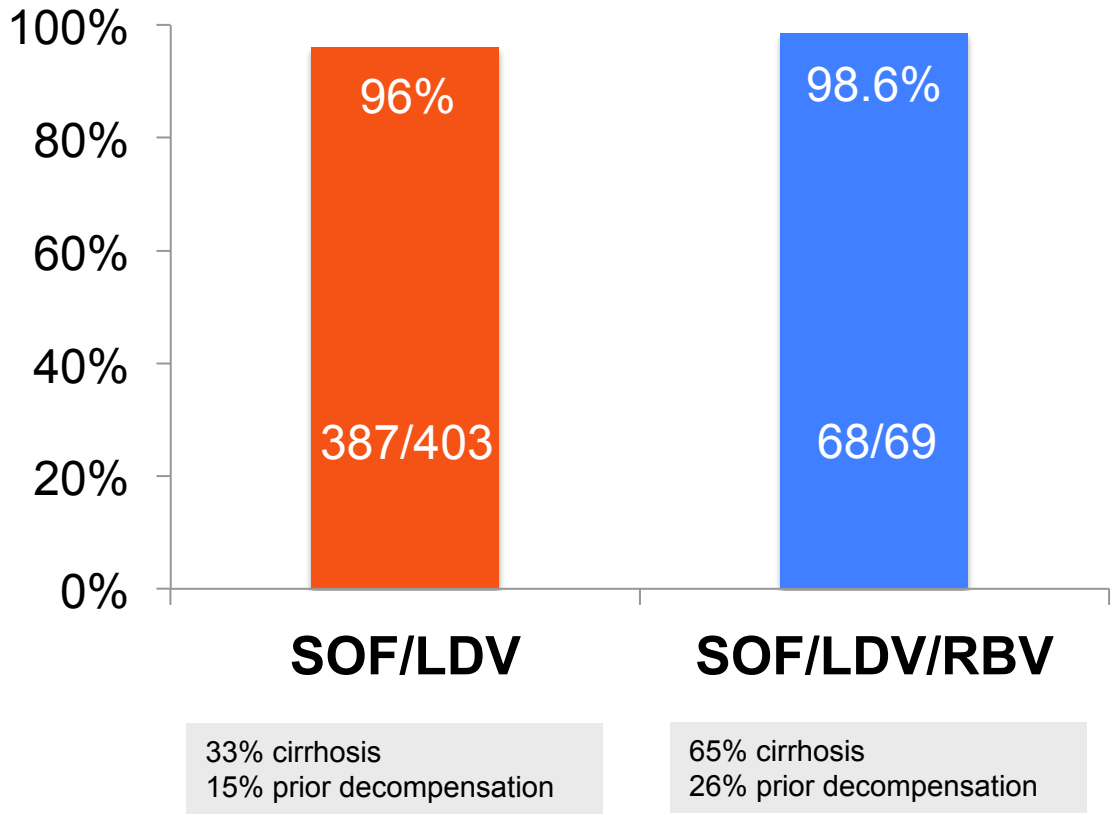
SVR12 Results with LDV/SOF±RBV for 8, 12, and 24 Weeks (Per Protocol Analysis)



SVR data in patients with G1b

Per Protocol Analysis* SVR12

* Efficacy population consists of patients who either completed the assigned regimen or discontinued due to AE or for virological reasons and have the virological outcome data available



33% cirrhosis
15% prior decompensation

65% cirrhosis
26% prior decompensation

Manns et al., APASL 2016

8 weeks versus 12 weeks SOF/LDV

Naive, no cirrhosis, HCV RNA < 6 Mio IU/mL*

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Applicability of Hepatitis C Virus RNA Viral Load Thresholds for 8-Week Treatments in Patients With Chronic HCV Genotype 1 Infection

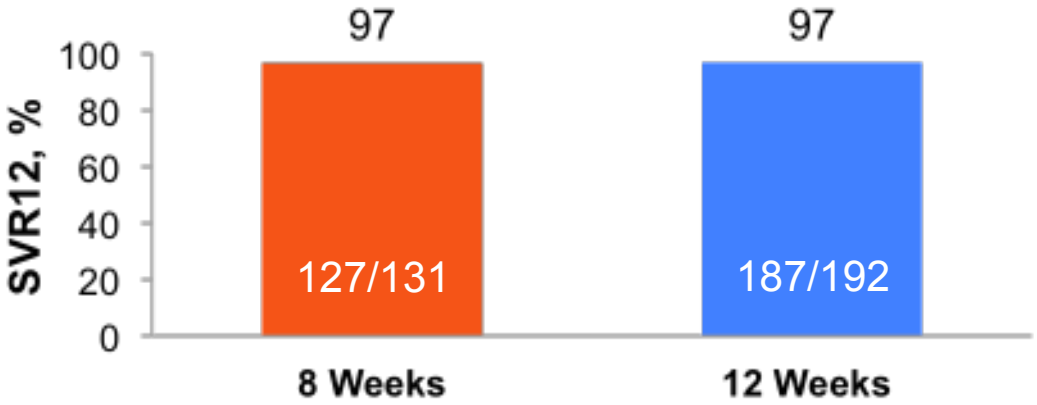
Johannes Vermehren,[1,a] Benjamin Maasoumy,[2,a] Raoel Maan,[3,4] Gavin Cloherty,[5] Caterina Berkowski,[1] Jordan J. Feld,[3] Markus Cornberg,[2] Jean-Michel Pawlotsky,[6,7] Stefan Zeuzem,[1] Michael P. Manns,[2] Christoph Sarrazin,[1,b] and Heiner Wedemeyer[2,b]

*seem to be not important in females

8 weeks or 12 weeks SOF/LDV?

323 Qualified for 8 Weeks Therapy*

42% received 8 weeks



*Qualified = Treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL

99/131 had available Week 4 HCV RNA

HCV4 BLOQ N=92 → SVR = 89, Relapse = 3

HCV4 QUANT N=7 (8%) → SVR = 7, Relapse = 0

133/192 had available Week 4 HCV RNA

HCV4 BLOQ N=117 → SVR = 114, Relapse = 3

HCV4 QUANT N=16 (12%) → SVR = 15, Relapse = 1

No role for response-guided therapy was identified

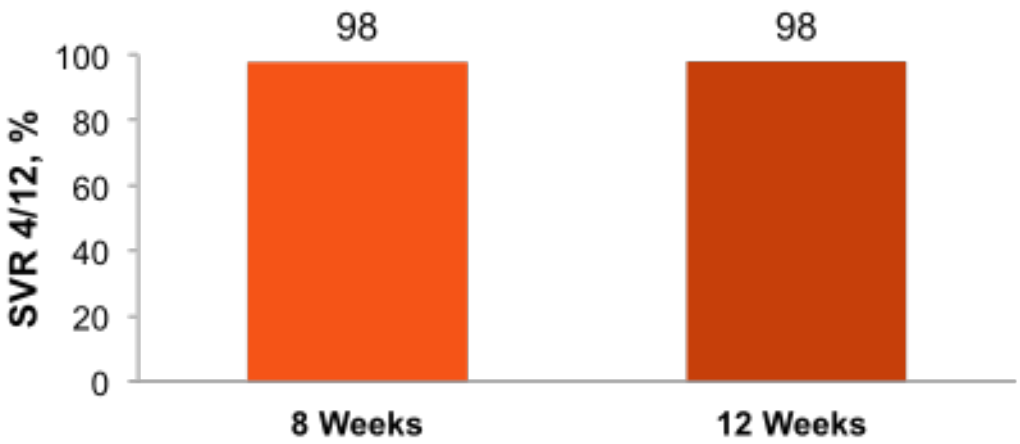
Terrault et al., AASLD 2015

SVR Among Those Who Qualified for 8 Week Treatment

423/2308 Qualified for 8 Weeks Therapy*

20% (86/423) received 8 weeks
74% (314/423) received 12 weeks
4% (18/423) received 24 weeks

SVR4/12 Interim Analysis

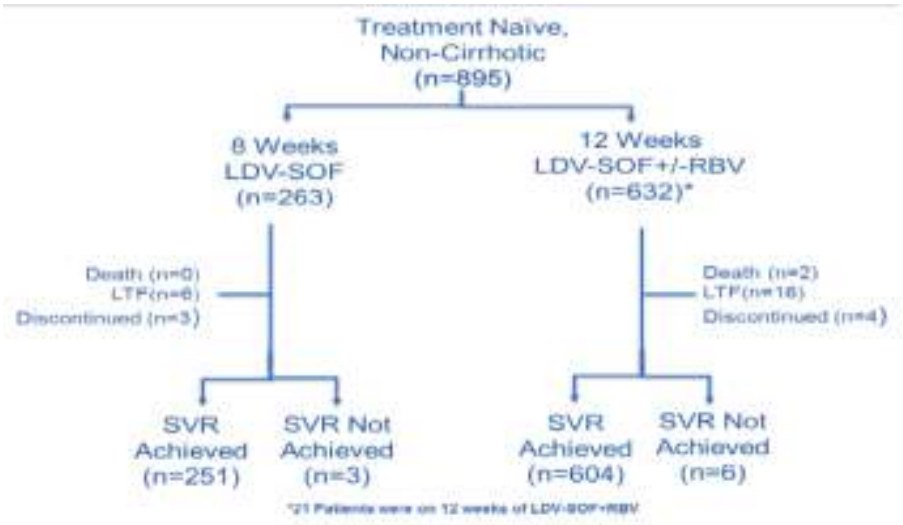


*Qualified = GT1, treatment-naïve, no cirrhosis, HCV RNA ≤ 6 million IU/mL

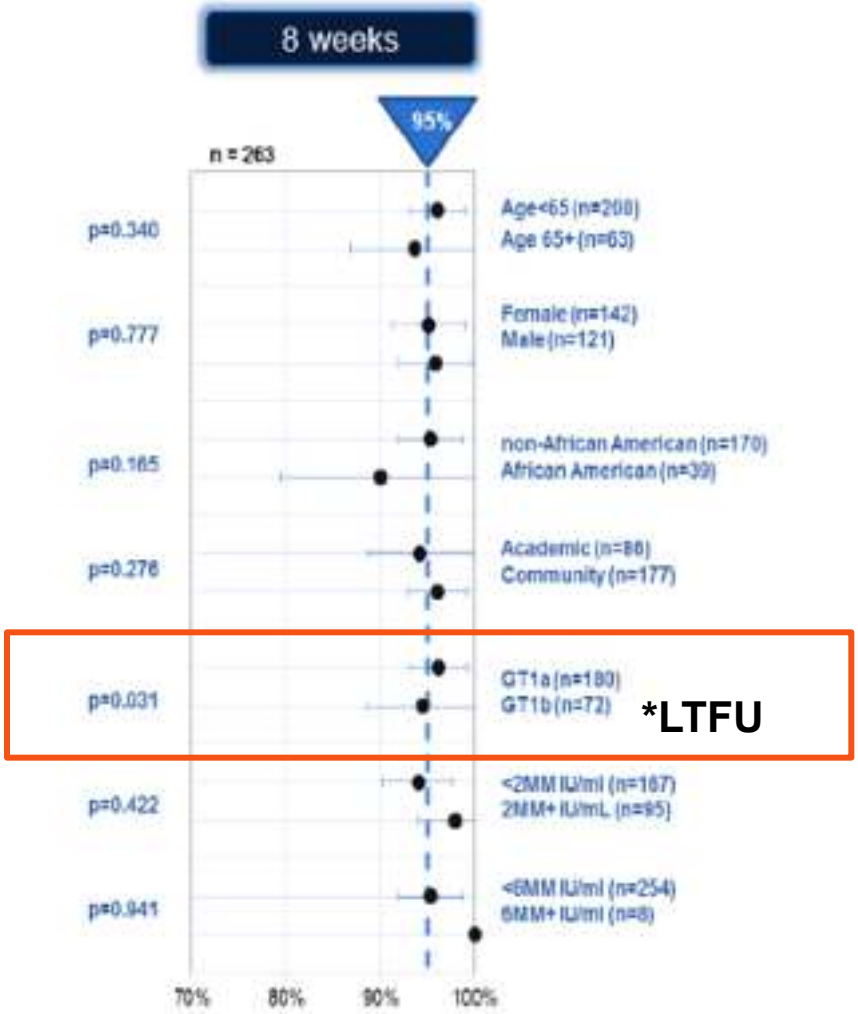
LDV/SOF 8 week is underused although it provides comparably high SVR12 rates in GT 1, TN, non-cirrhotic patients with baseline HCV RNA ≤ 6 million IU/mL

8 weeks or 12 weeks SOF/LDV?

Trio Health

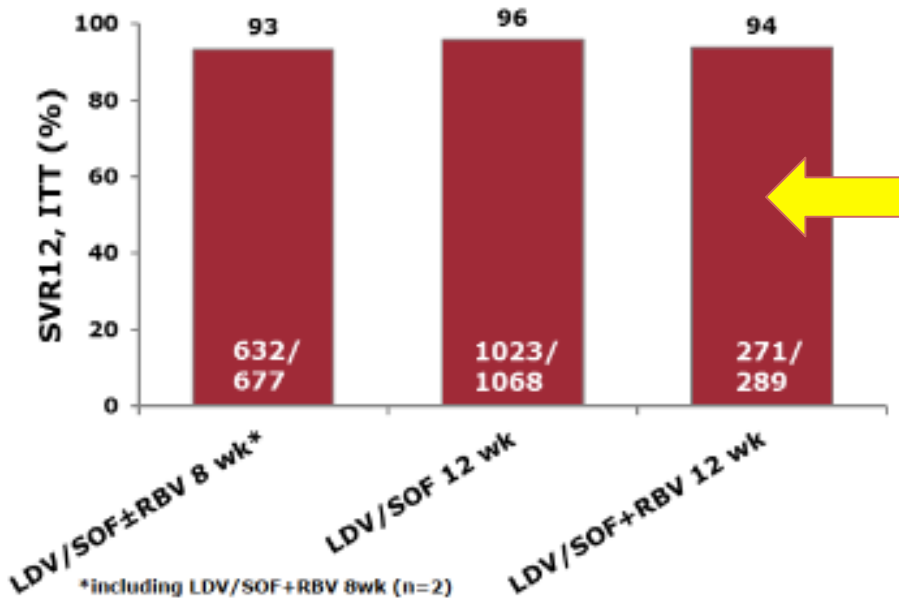


95% 96%



Real-Word Efficacy of SOF/LDV in Germany

SVR12 rates (Intention-to-Treat)



69.3% liver cirrhosis
67% treatment experienced

N=59 with HIV
SVR 96.6%

SVR12 rates (Per-Protocol)

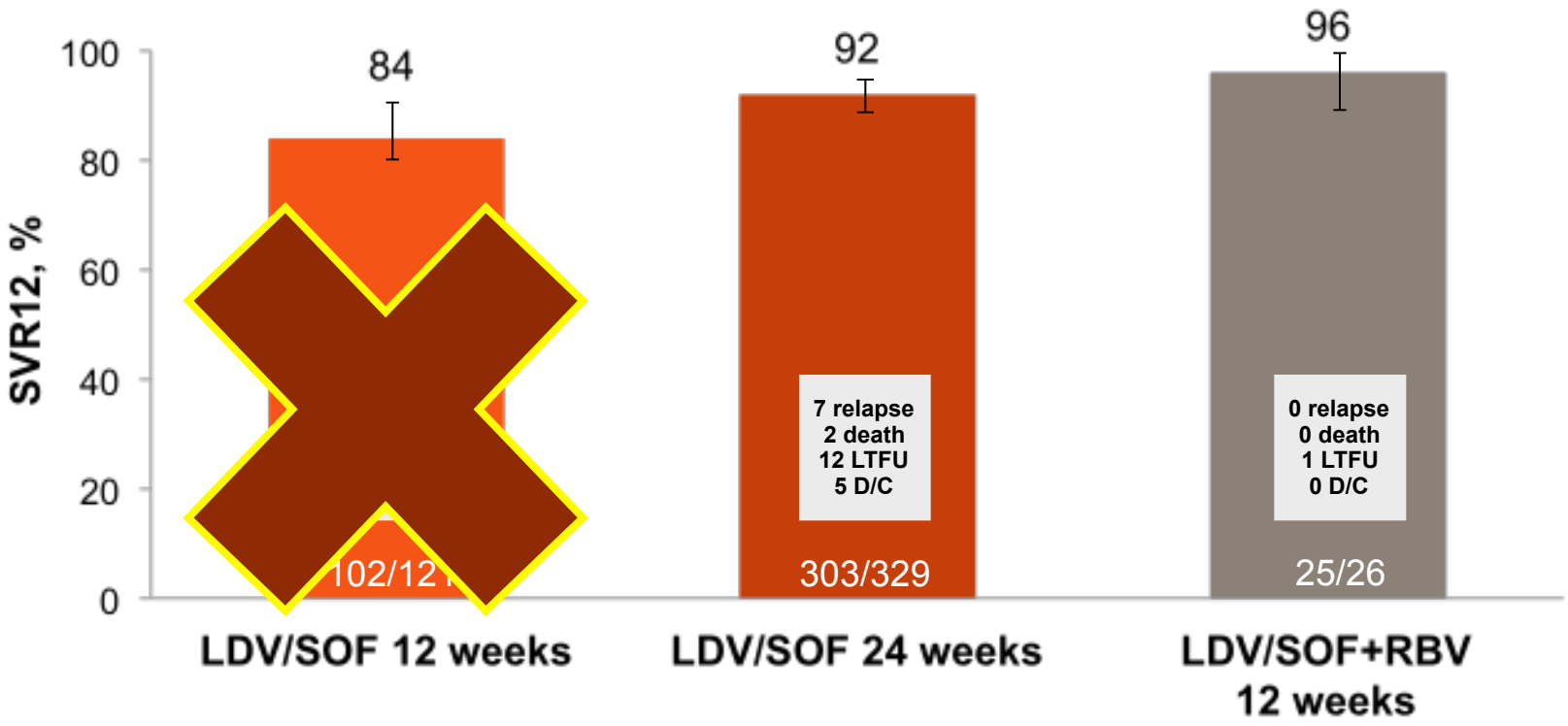
Treatment regimen	SVR, PP n/total (%)	Discontin. n/total (%)	Relapse/NR n/total (%)
LDV/SOF±RBV 8 wk*	631/644 (98)	0/644 (-)	13/644 (2)#
LDV/SOF 12 wk	1021/1033 (99)	2/1033 (<1)	10/1033 (<1)##
LDV/SOF+RBV 12 wk	271/279 (97)	0/279 (-)	0/279 (-)

* including LDV/SOF+RBV 8 wk (n=2), #9 relapses, ## 10 relapses

Buggisch et al., EASL 2016

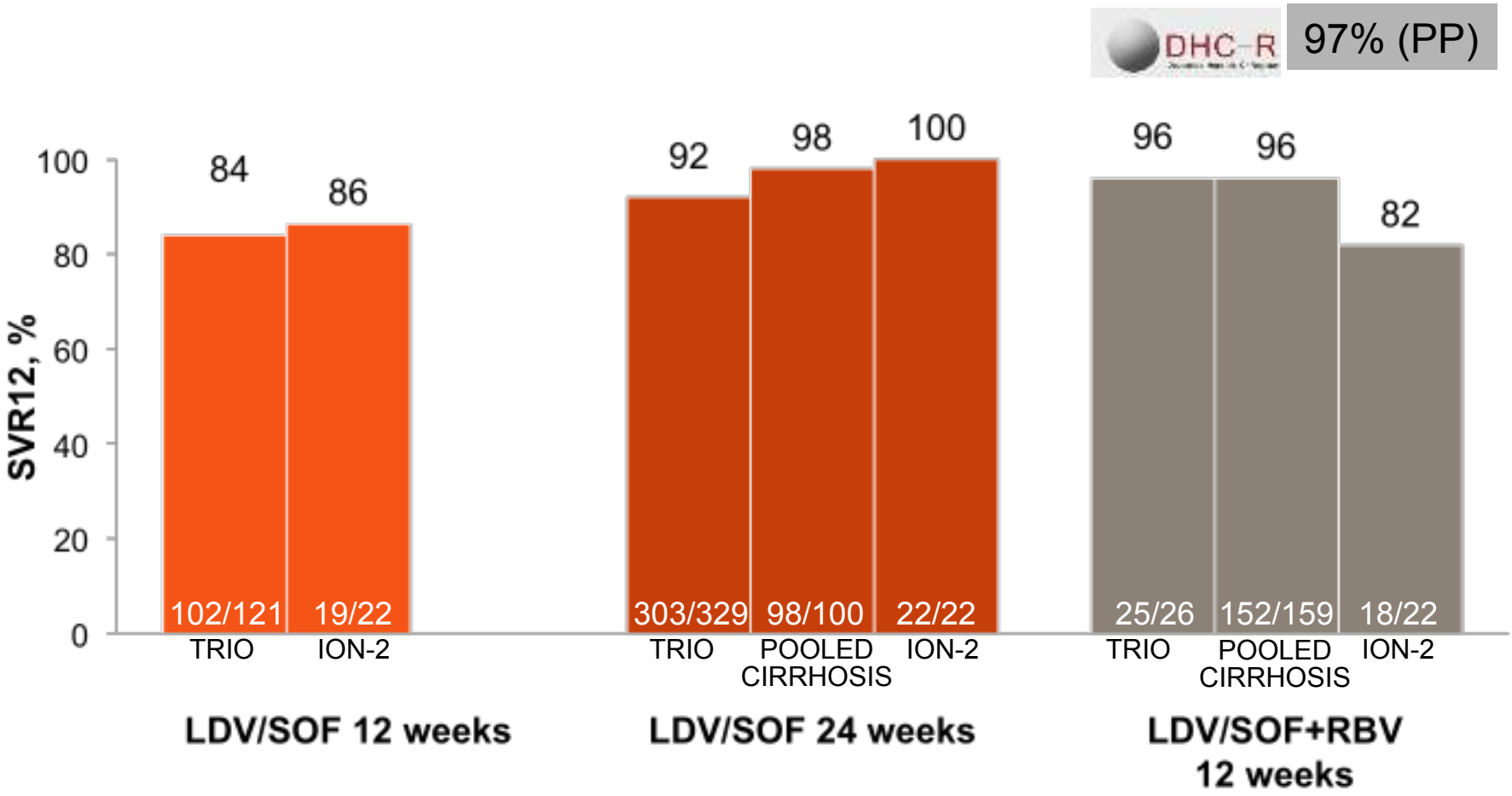
When do we need RBV or 24 weeks SOF/LDV?

TRIO Real-World Cohort: LDV/SOF±RBV for 12 or 24 Weeks in **Treatment-Experienced, Cirrhotic GT 1 HCV**



Overall discontinuation rate was 1% (5/476)

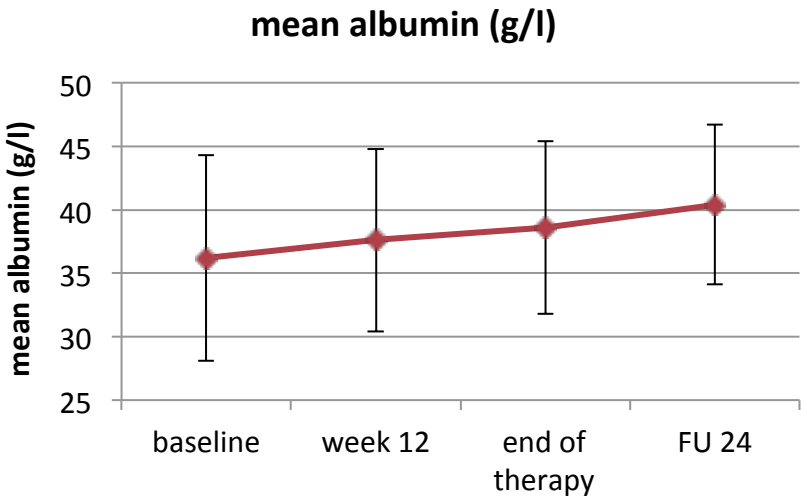
Summary of LDV/SOF±RBV in GT1
Treatment-Experienced Cirrhotics

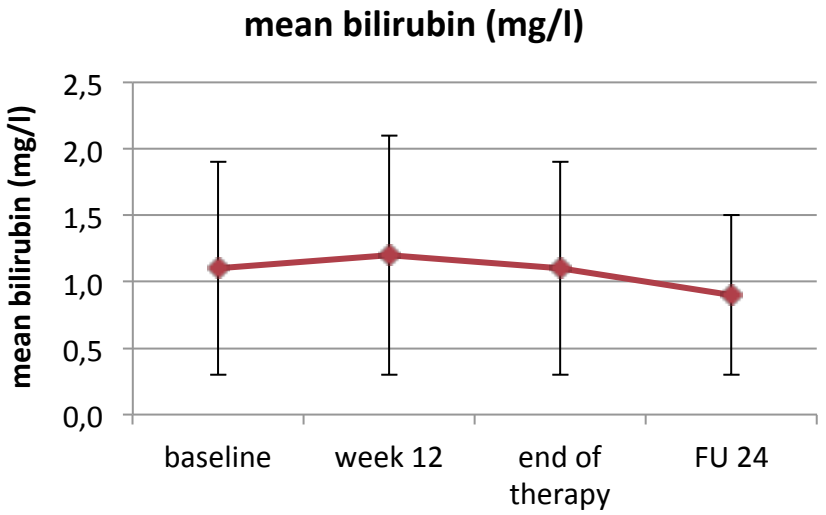


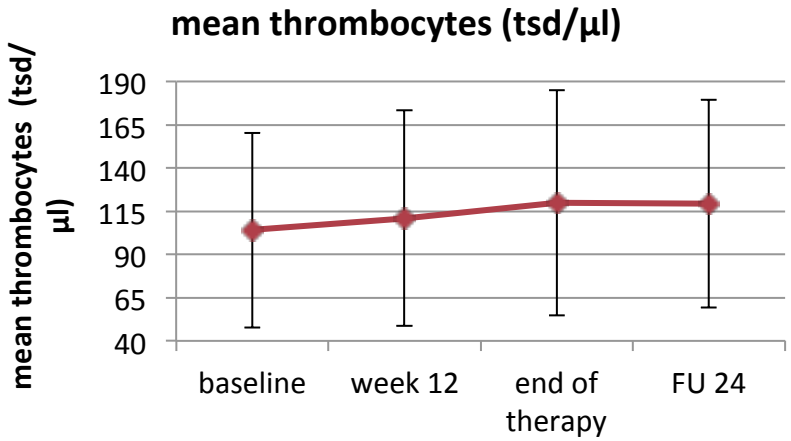
Curry, AASLD, 2015, 1108. Afdhal N, et al. *New Engl J Med*. 2014. Published online April 12, 2014.
Reddy K .,et al. *Hepatology*. Published Online April 2015

What do we achieve with SVR in advanced fibrosis and cirrhosis?

Improvement of liver function parameters in the German Hepatitis C-Registry (DHC-R)







- **632 patients with advanced HCV-associated liver cirrhosis**
- **Child A 72%, Child B 13%, Child C 1.2%**
- **Ascites at screening 38%**

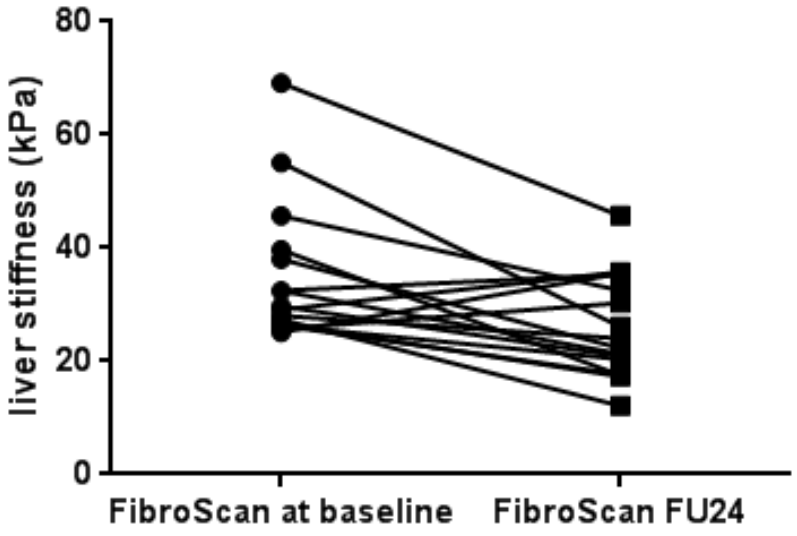
Deterding et al., EASL 2016

Medizinische Hochschule Hannover

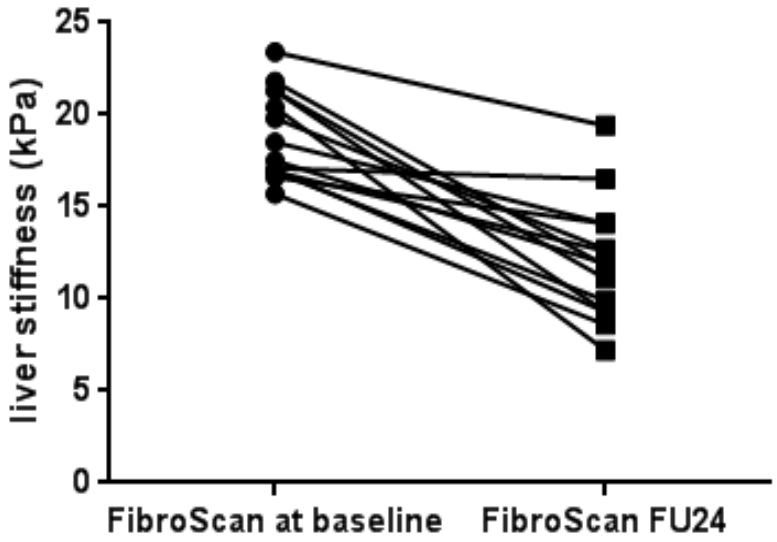
Improvement of liver stiffness values by successful IFN-free antiviral therapy: Fibroscan

Different DAA regimens at Hannover Medical School

FibroScan > 25 kPa at baseline

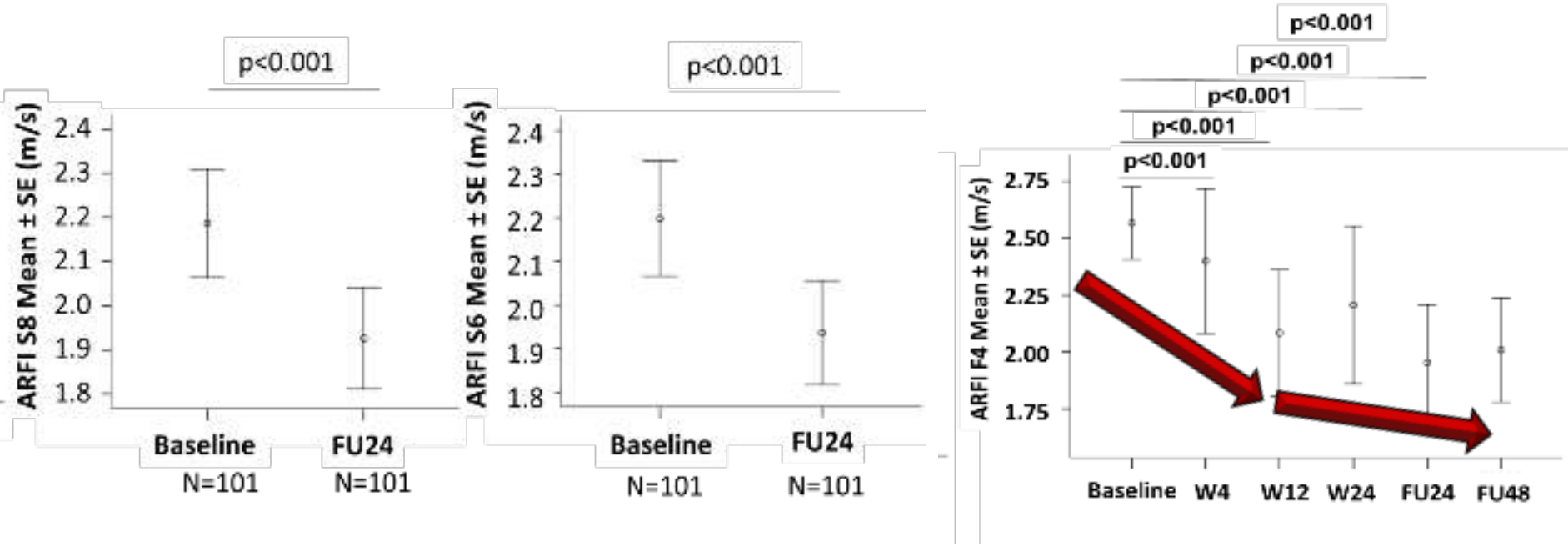


FibroScan ≤ 25 kPa at baseline



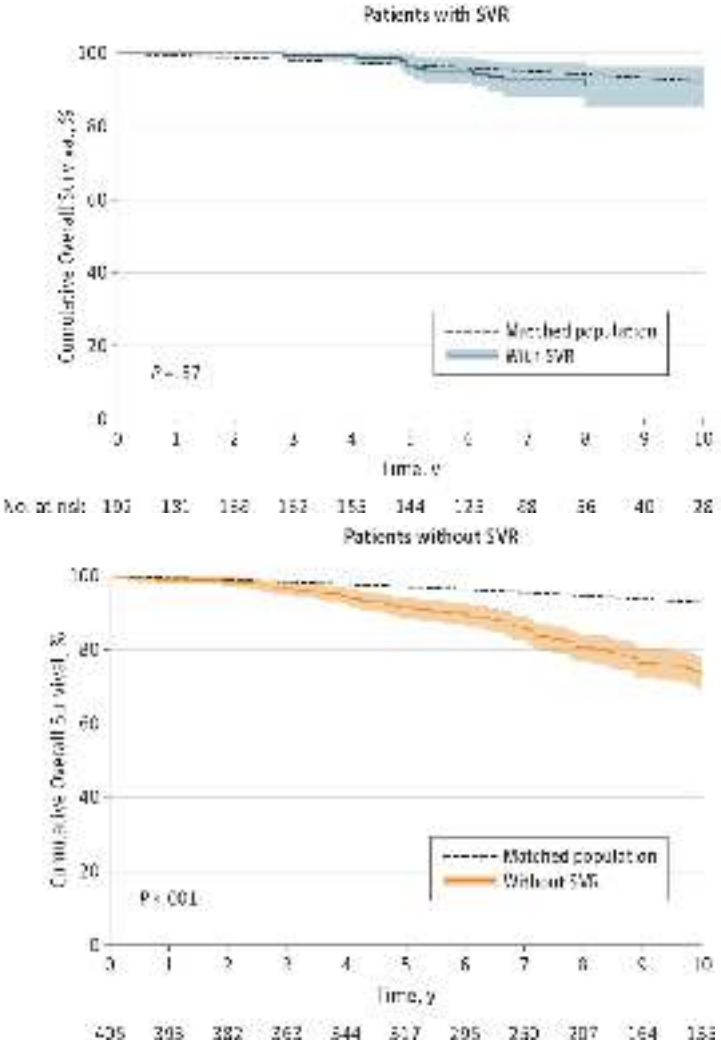
Improvement of liver stiffness values by successful IFN-free DAA therapy: **ARFI**

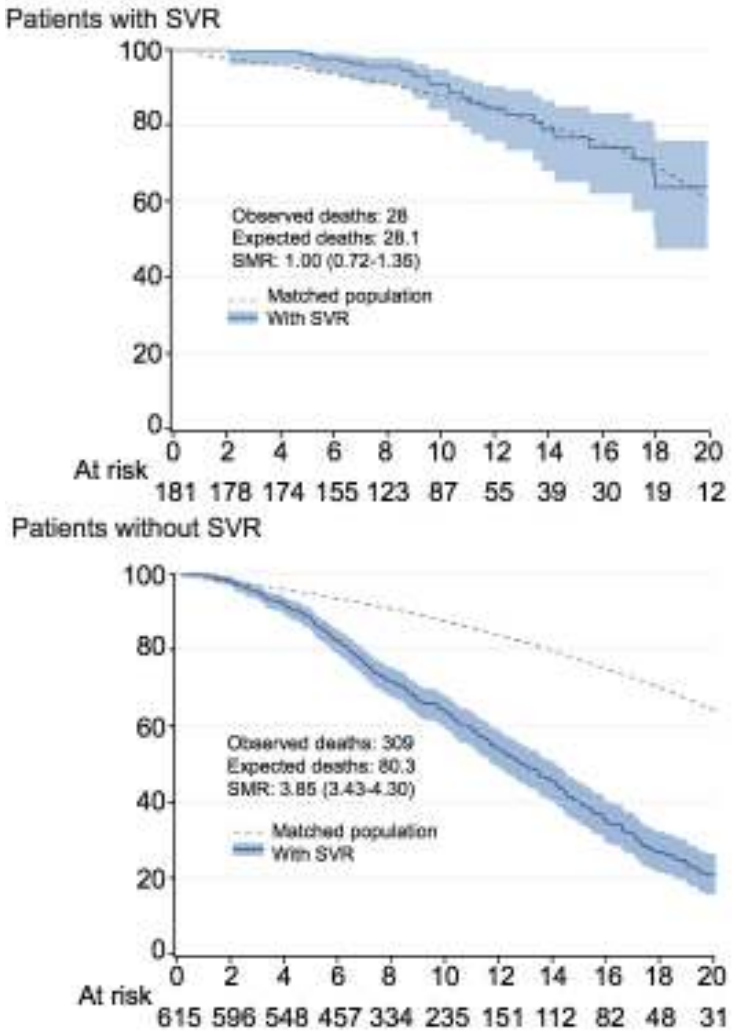
Different DAA regimens at Hannover Medical School



Attia et al.; EASL 2016

Patients with advanced fibrosis* or cirrhosis** who clear **HCV** infection have a survival similar to the general population!



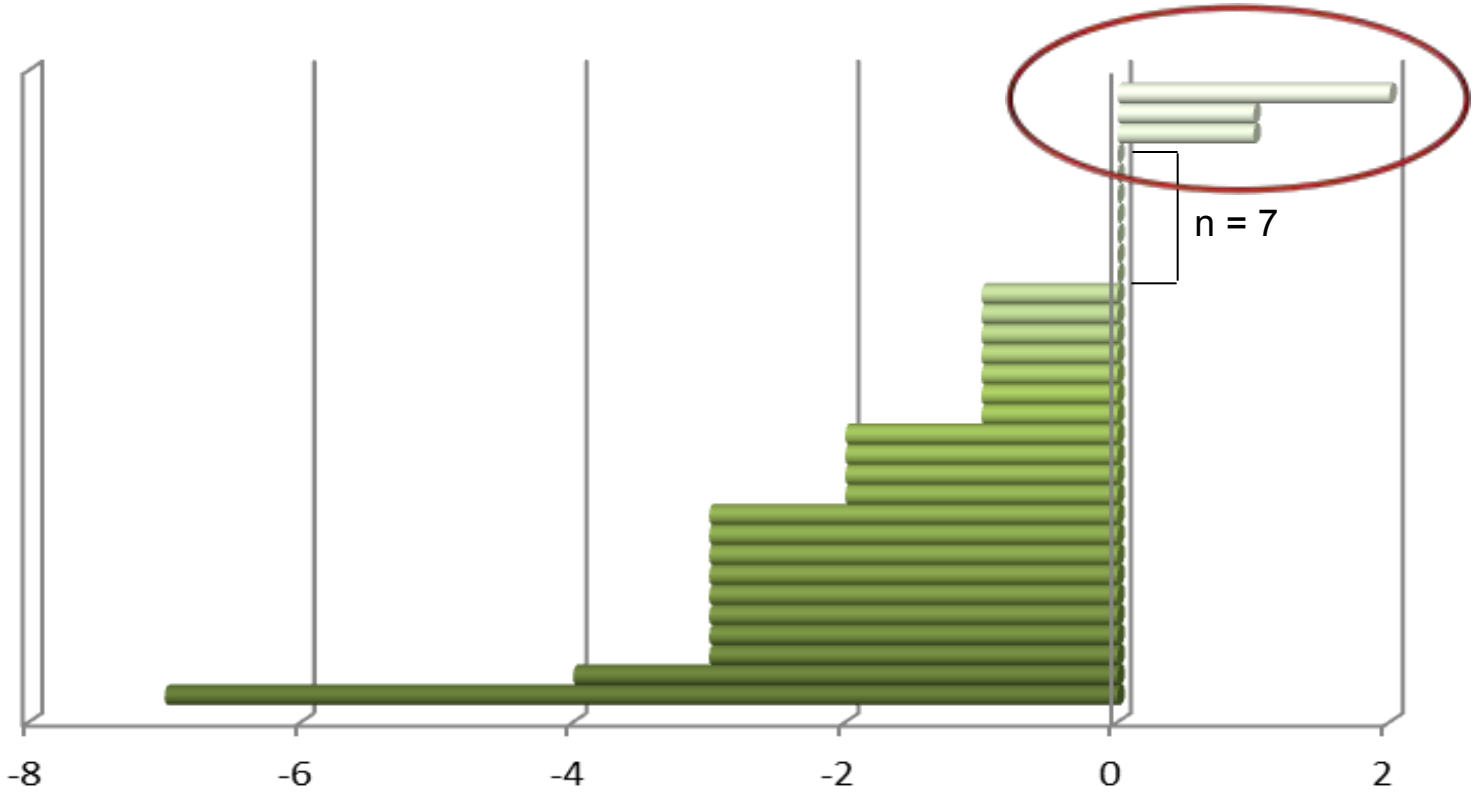


*Van der Mer et al., JAMA. 2014 Nov 12;312(18):1927-8.
** Bruno et al., J Hepatol. 2016 Mar 23. pii: S0168-8278(16)00075-1.

Improvement of MELD Score from baseline to FU 12 (Child B/C) n = 31

Data from Hannover Medical School

point of no return? → future research



* including relapse patients documented at the timepoint of relapse

HCC risk remains in patients with liver cirrhosis

HCC surveillance after SVR is important!

J Hepatol. 2016 Apr 12. pii: S0168-8278(16)30113-1. doi: 10.1016/j.jhep.2016.04.008. [Epub ahead of print]

Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution.

Reig M[1], Mariño Z[2], Perelló C[3], Iñarrairaegui M[4], Ribeiro A[1], Lens S[2], Díaz A[5], Vilana R[6], Darnell A[6], Varela M[7], Sangro B[4], Calleja JL[3], Forns X[2], Bruix J[8].

HIGH RISK FOR HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS WITH SVR FOLLOWING IFN-FREE DAA TREATMENT WITHIN ONE YEAR FOLLOW-UP.

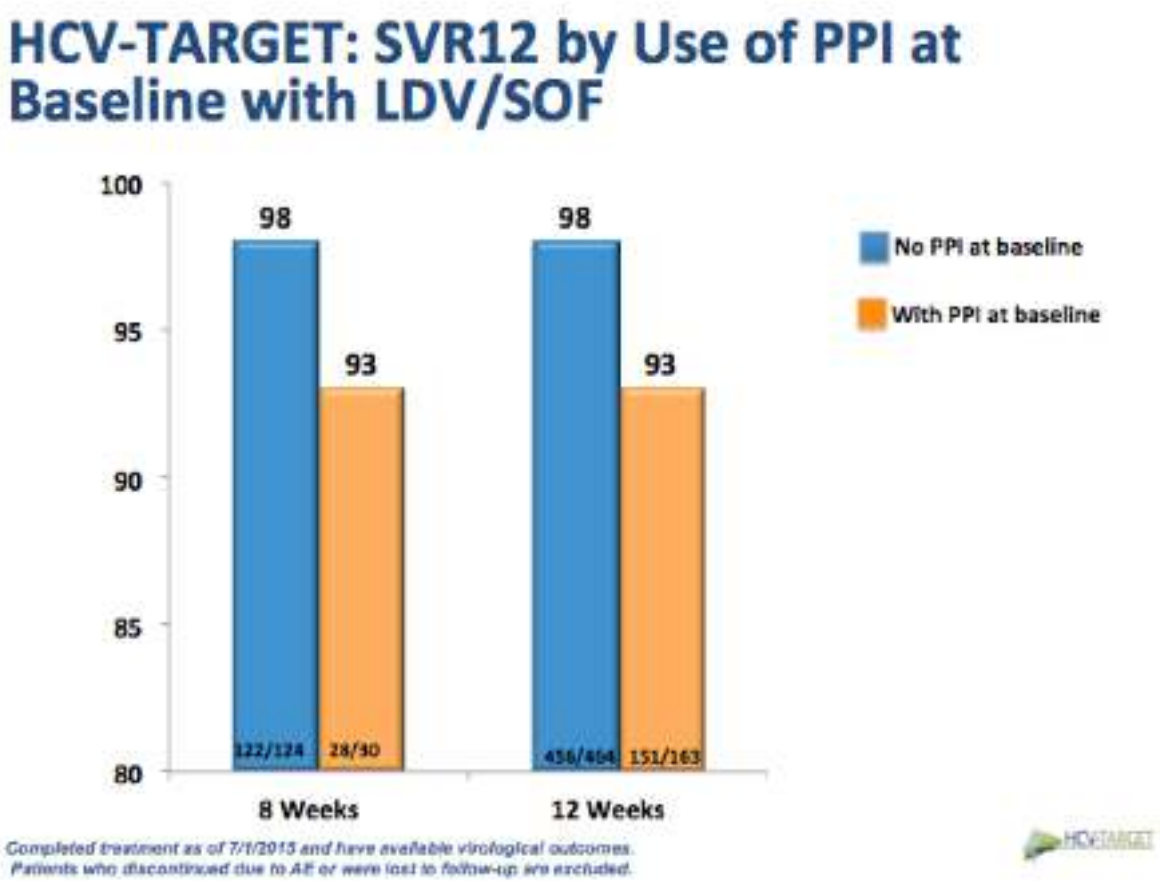
Karin Kozbial[1], Stephan Moser[2], Remy Schwarzer[3], Hermann Laferl[4], Ramona Al-Zoairy[5], Rudolf Stauber[6], Albert F. Stättermayer[1], Clarissa Freissmuth[1], Rafael Stern[1], Sandra Beinhardt[1], Andreas Maieron[3], Ivo Graziadei[7], Michael Gschwantler[2], Wolfgang Vogel[8], Heinz Zoller[8], Peter Ferenci[1], Harald Hofer[1]

Safety / DDI Issues in the real world

HARVONI: SUMMARY OF PRODUCT CHARACTERISTICS, PAGE 8

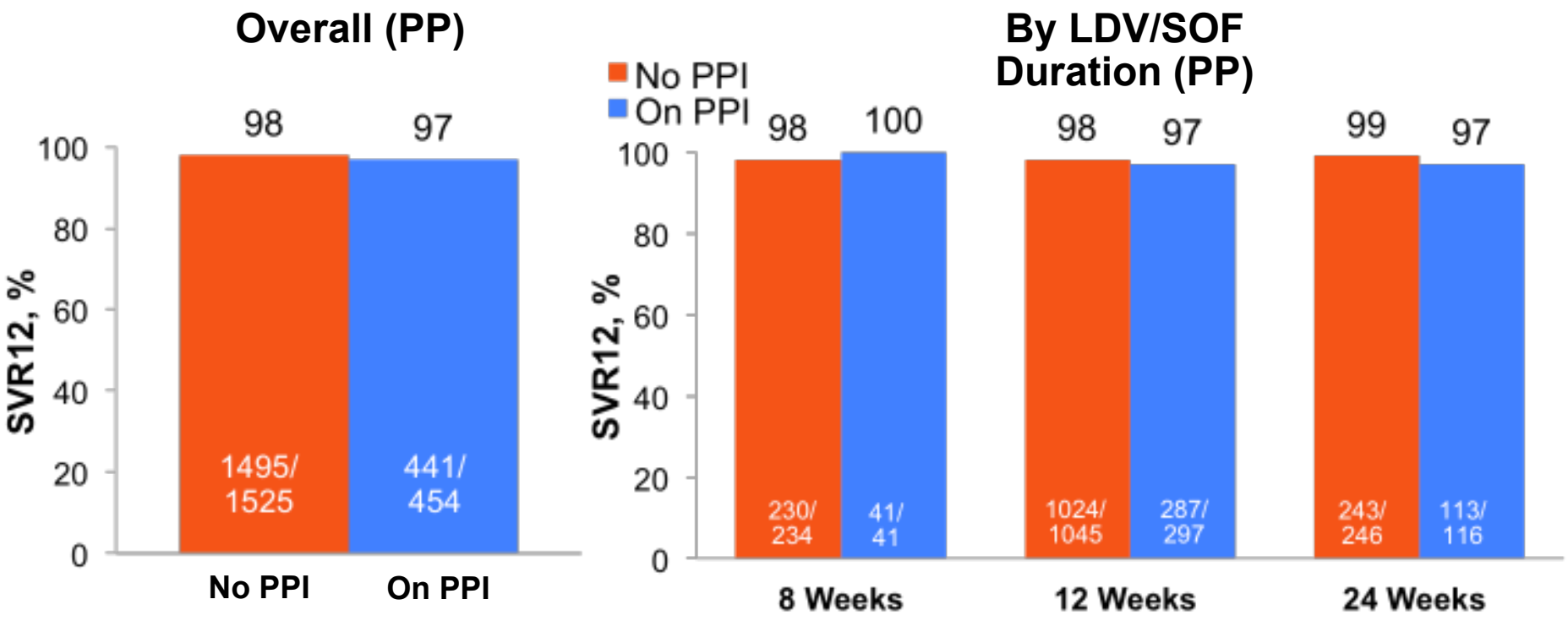
Proton pump inhibitors		
Omeprazole (20 mg once daily)/ ledipasvir (90 mg single dose)[c]/ sofosbuvir (400 mg single dose)[c] Omeprazole dosed simultaneously with Harvoni Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e]	Ledipasvir ↓ C_{max} 0.89 (0.61, 1.30) ↓ AUC 0.96 (0.66, 1.39) Sofosbuvir ↔ C_{max} 1.12 (0.88, 1.42) ↔ AUC 1.00 (0.80, 1.25) GS-331007 ↔ C_{max} 1.14 (1.01, 1.29) ↔ AUC 1.03 (0.96, 1.12) (Increase in gastric pH)	Proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with Harvoni. Proton pump inhibitors should not be taken before Harvoni.

PPI use and efficacy of SOF/LDV



Terrault et al., AASLD 2015

No effect of PPI use on LDV/SOF SVR in GT1 Patients in the TRIO cohort



- Lower SVR in patients with twice daily PPI use (*98% versus 91%; p=0.03*)

Daily PPI use did not have an effect on SVR in a heterogeneous real-world US population **when used according to LDV/SOF US prescribing information**

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another Direct Acting Antiviral drug

For full details of all interactions, see www.hep-druginteractions.org .

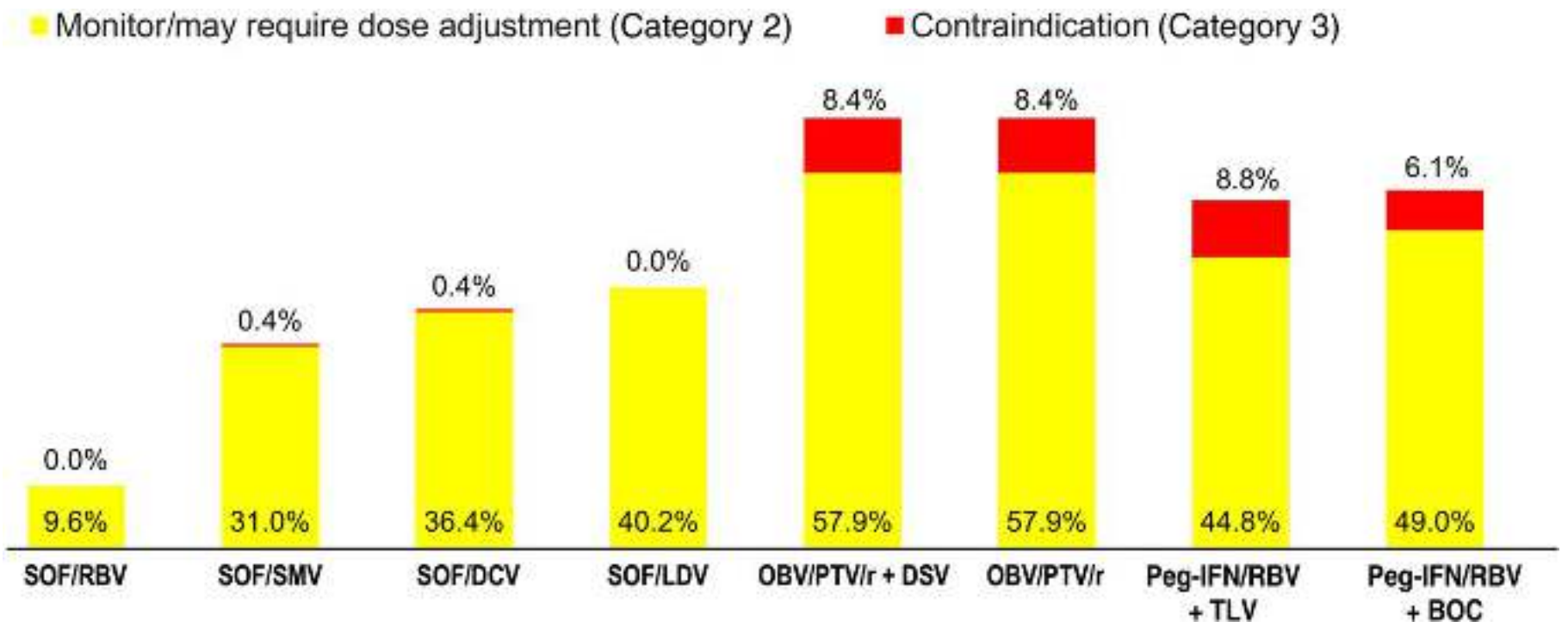
Description of the interactions

Drugs that should not be coadministered (RED)

Ledipasvir/Sofosbuvir + Amiodarone
Coadministration is not recommended. Coadministration of ledipasivr/sofosbuvir with amiodarone may result in serious symptomatic bradycardia. The mechanism of this effect is unknown.

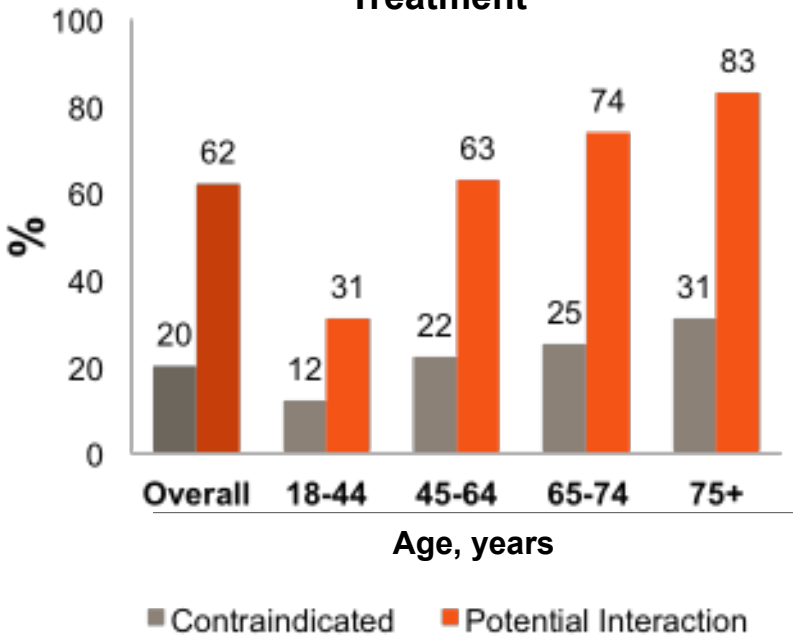
Proportion of patients with significant drug–drug interactions (DDIs) between their regular outpatient medications and direct-acting antiviral agent (DAA)–containing regimens.

N=261 patients treated with DAA at Hannover Medical School (no transplant patients)

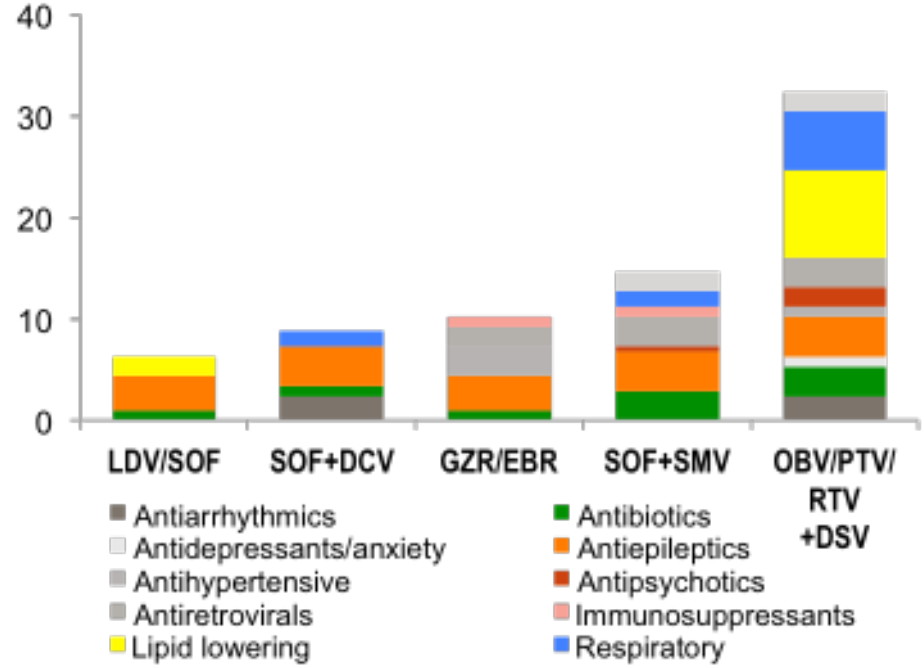


Comorbidities, Comedication and Potential DDIs in CHC Patients in Spain

Proportion of Patients on Co-Medication with Potential DDI to at Least One of Chronic HCV Treatment



Potential Contraindications According to Antiviral Therapy Received

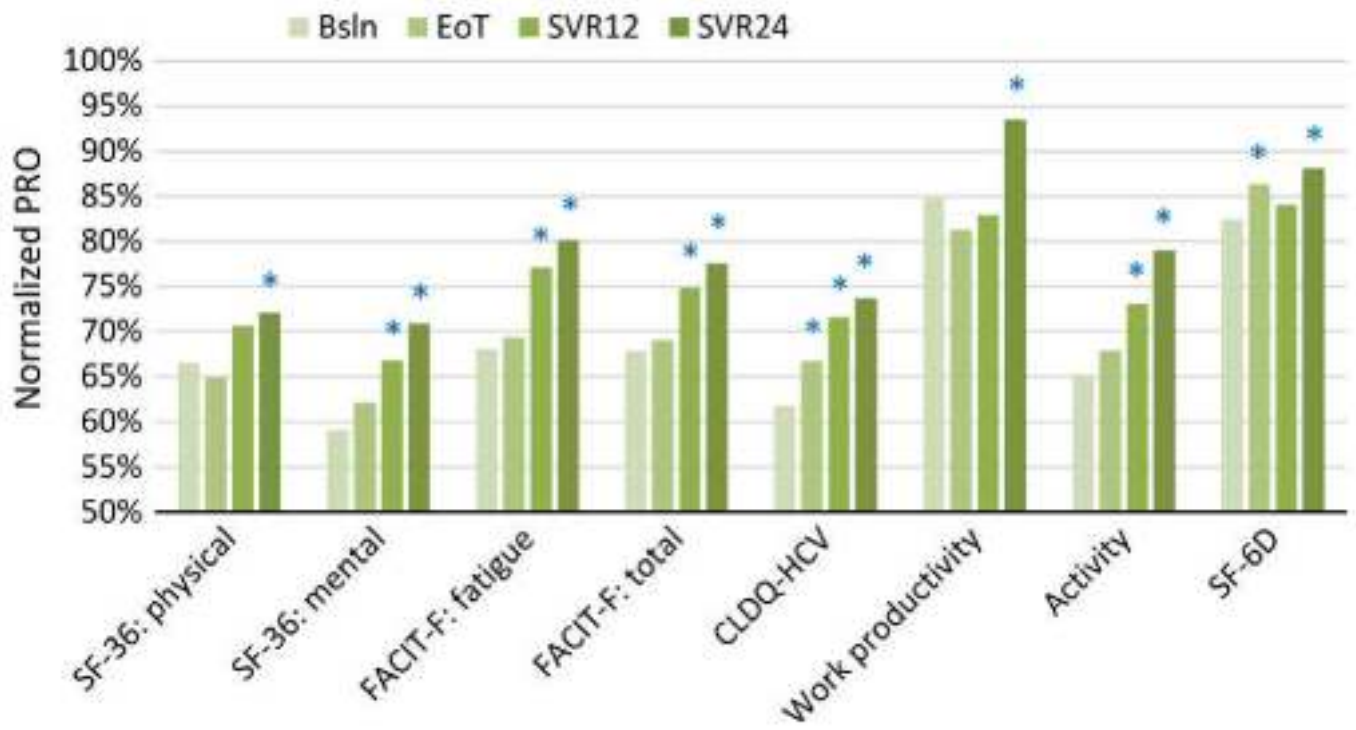


HCV infection is associated with high comorbidity and use of concomitant medication, especially in older patients. Due to differences in DDI potential among HCV regimens, prescribers need to carefully select the appropriate DAA.

Sicras et al., EASL 2016

Improvement of patients related outcome during and after DAA treatment

Sofosbuvir 400 mg 1/d
Ledipasvir 90 mg 1/d
± Ribavirin



Younossi ZM et al., Liver Int. 2015 Jun 9. doi: 10.1111/liv.12886.

Answers:

1. SVR with SOF/LDV in the real-world is comparable to phase III data
2. 8-week SOF/LDV treatment in naive patients without cirrhosis and VL <6 Mio IU/ml is effective but underused
3. Treatment experienced patients with cirrhosis should receive 12 weeks plus RBV or 24 weeks if RBV is/was problematic
4. SVR in patients with advanced fibrosis and cirrhosis improves survival.

→ Don‘t forget HCC surveillance in patients with SVR and cirrhosis

5. SOF/LDV is very safe if the physician and patient are compliant with the label and recommendations.

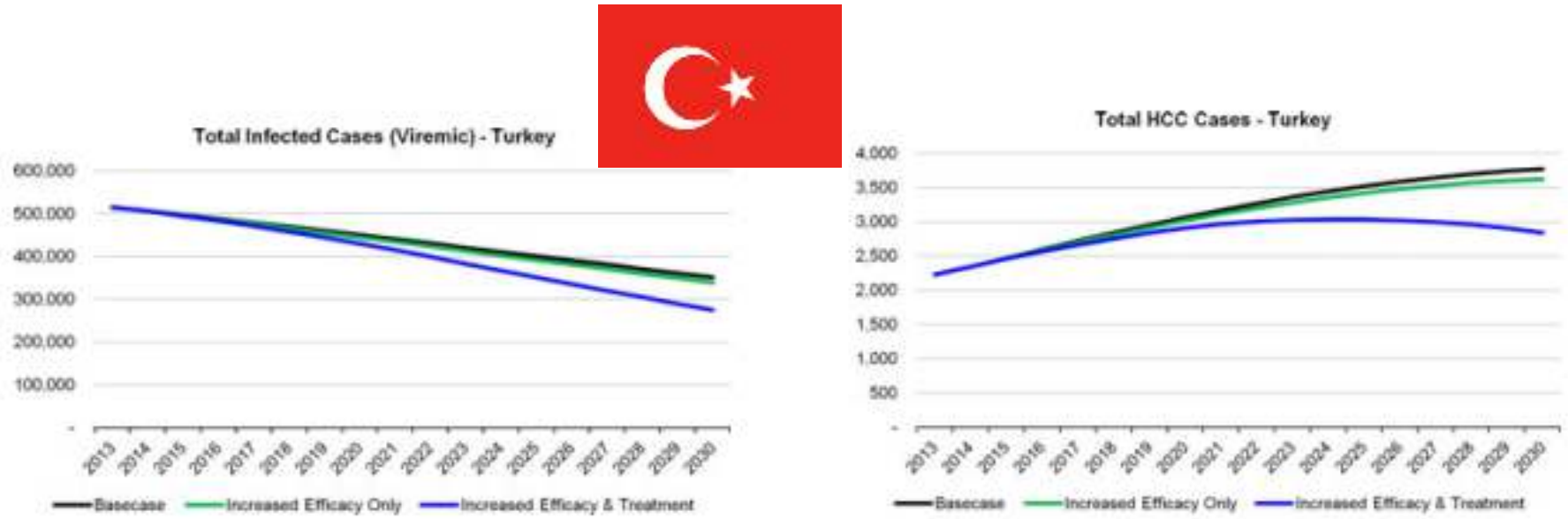

HEPATITIS C
IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LETS FINISH HIM OFF!...
MIKE LUCKOVICH 2004

Challenge: Eradication of HCV in Germany and world-wide

- With the better safety profile of interferon-free therapies, eligibility for HCV treatment will expand broadly*
  - Prerequisite for Eradication of HCV: Increase of treatment uptake**
  - Obstacle: Costs, Re-Infection in in risk groups
    up to 33% in special situations (MSM and drugs)
    Systematic Review by Hagan et al., AIDS. 2015 Nov;29(17):2335-45
- Eradication of an infectious disease was so far not possible without a vaccine ... *(Chris Walker et al., Current Opinion Immunol 2015)*

*Höner zu Siederdissen, ..., Cornberg. Liver Int. 2015 Jul;35(7):1845-52.
** Wedemeyer, ..., Cornberg et al., J Viral Hepat. 2014 May;21 Suppl 1:60-89

Strategies to manage hepatitis C virus (HCV) disease burden

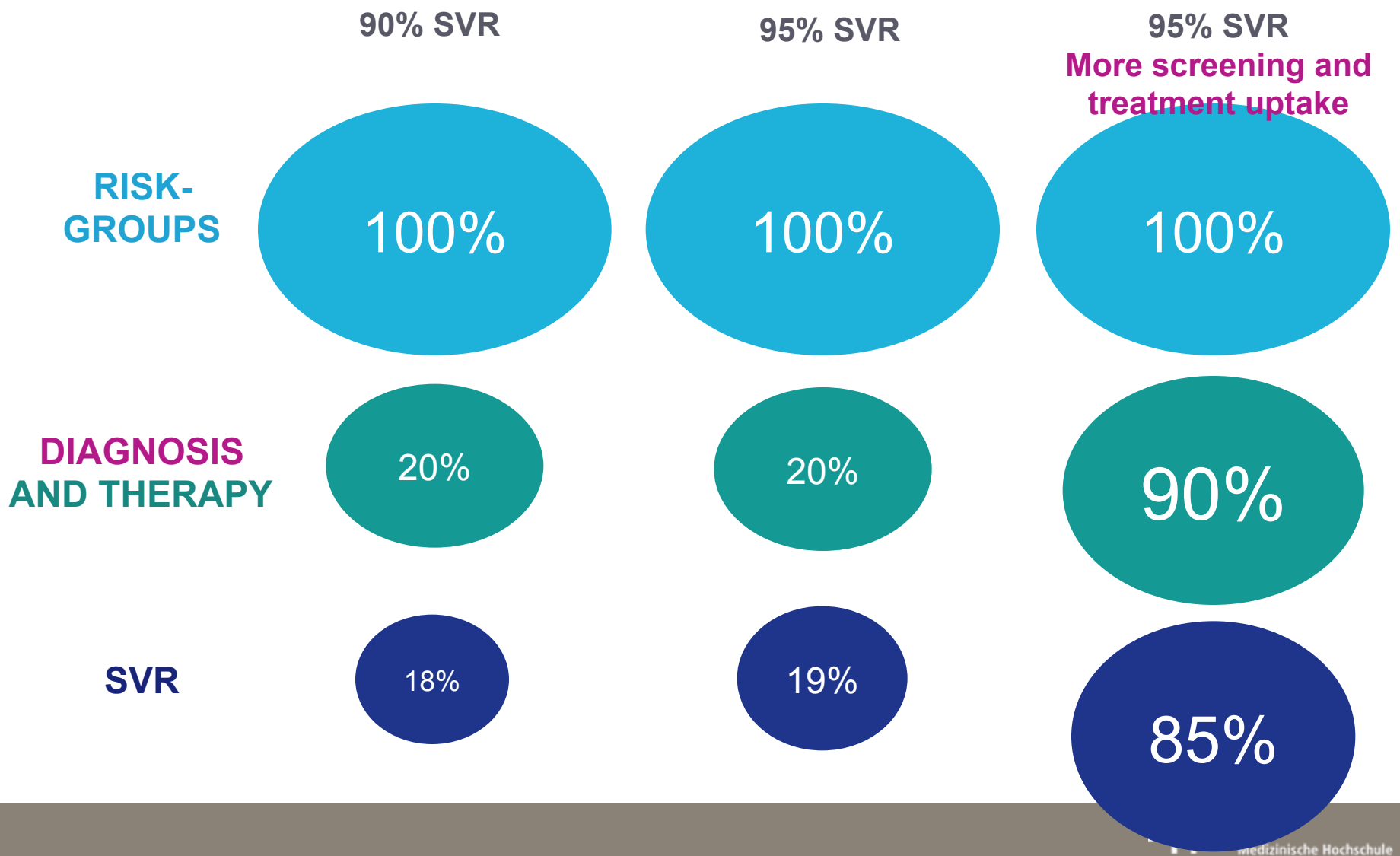


Old standard Peg-IFN/RBV

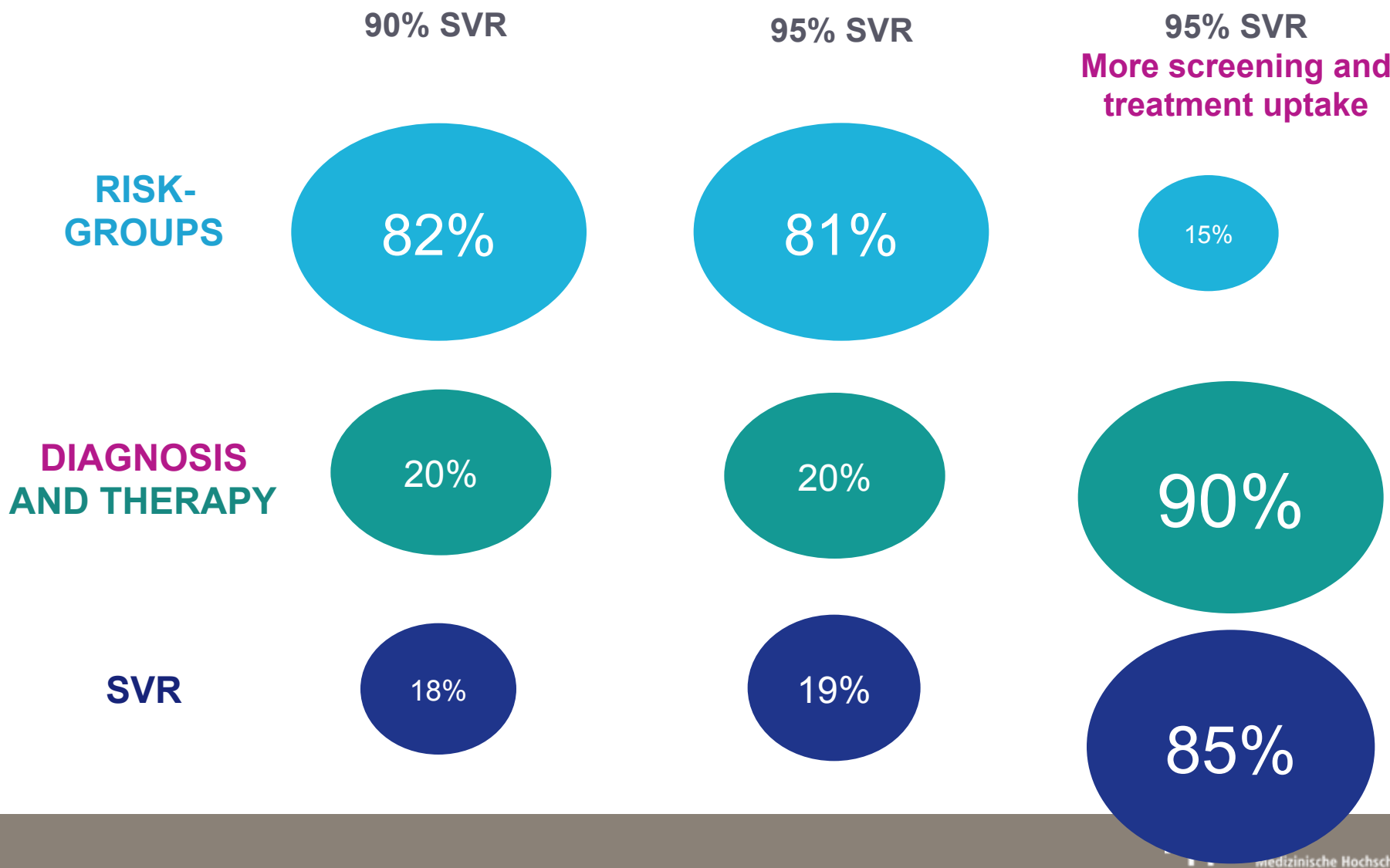
SVR 90% with DAA but no increase treatment uptake

SVR 90%, Increase of Treatment uptake by 75%

Screening and treatment uptake is more important than SVR 90% versus 95%

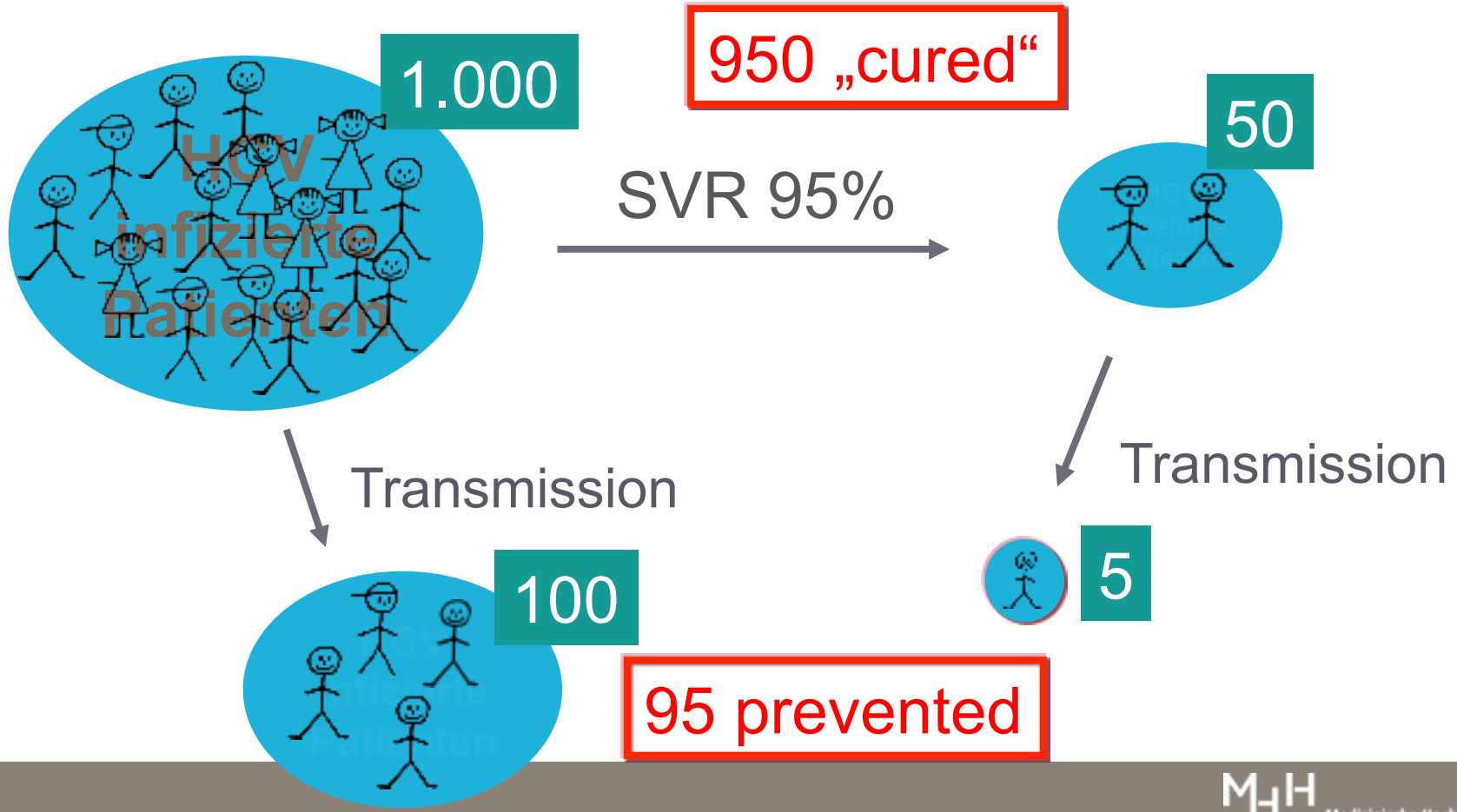


Screening and treatment uptake is more important than SVR 90% versus 95%



SVR >100% ???

1.000 treated → 1.045 infections cured / prevented (104,5%)



Conclusion HCV

- Hepatitis C is curable – in >90% of patients → Cure reduces overall mortality
- IFN free therapies are possible for most of the patients
- Now it will be important to increase treatment uptake to have an impact on overall mortalilty and HCC incidence