Νεότερες θεραπευτικές εξελίξεις

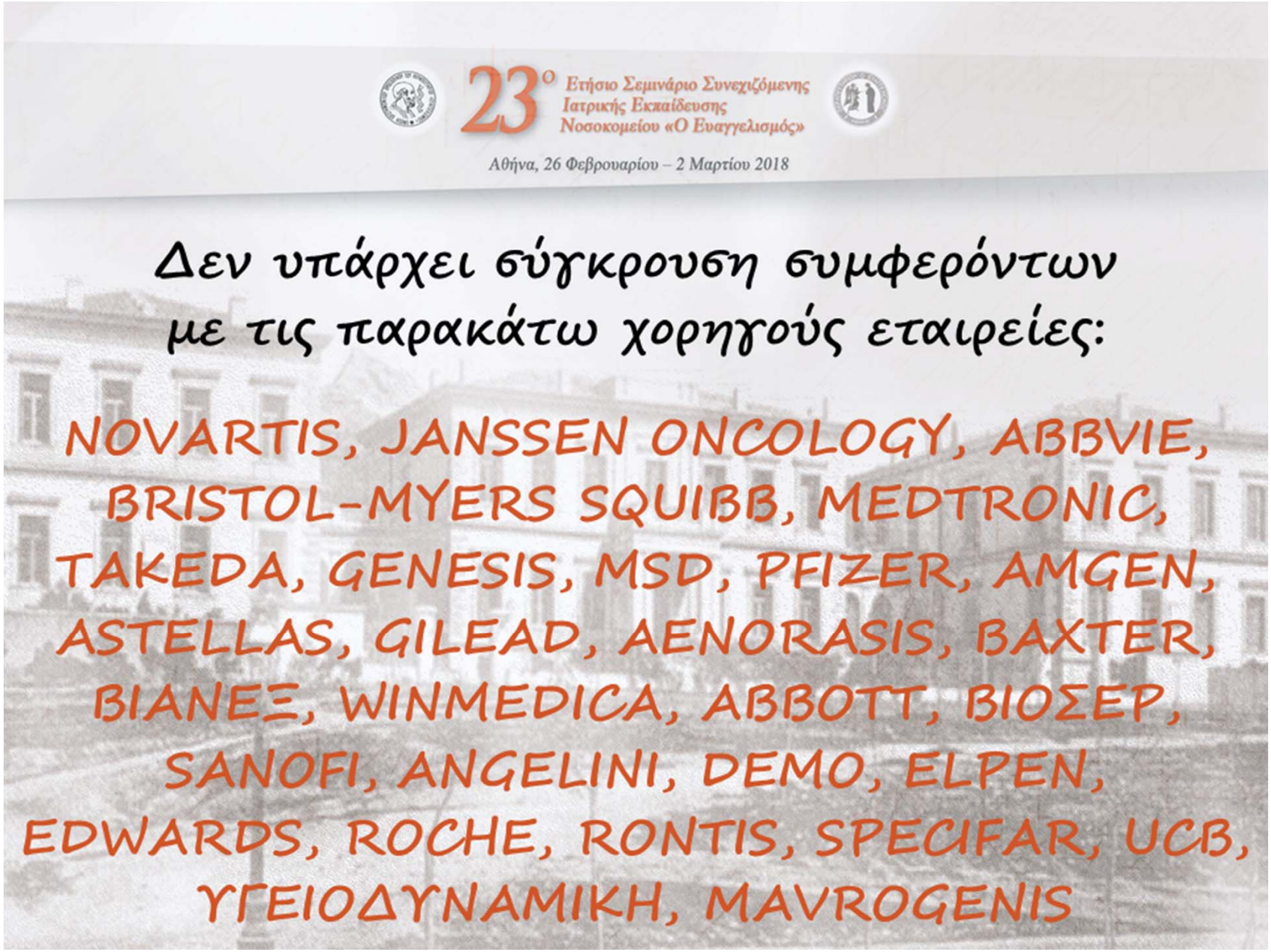
Δρ. Βασίλειος Α. Σεβαστιανός

Δ’ Παθολογική Κλινική

Γ.Ν.Α «Ο Ευαγγελισμός»

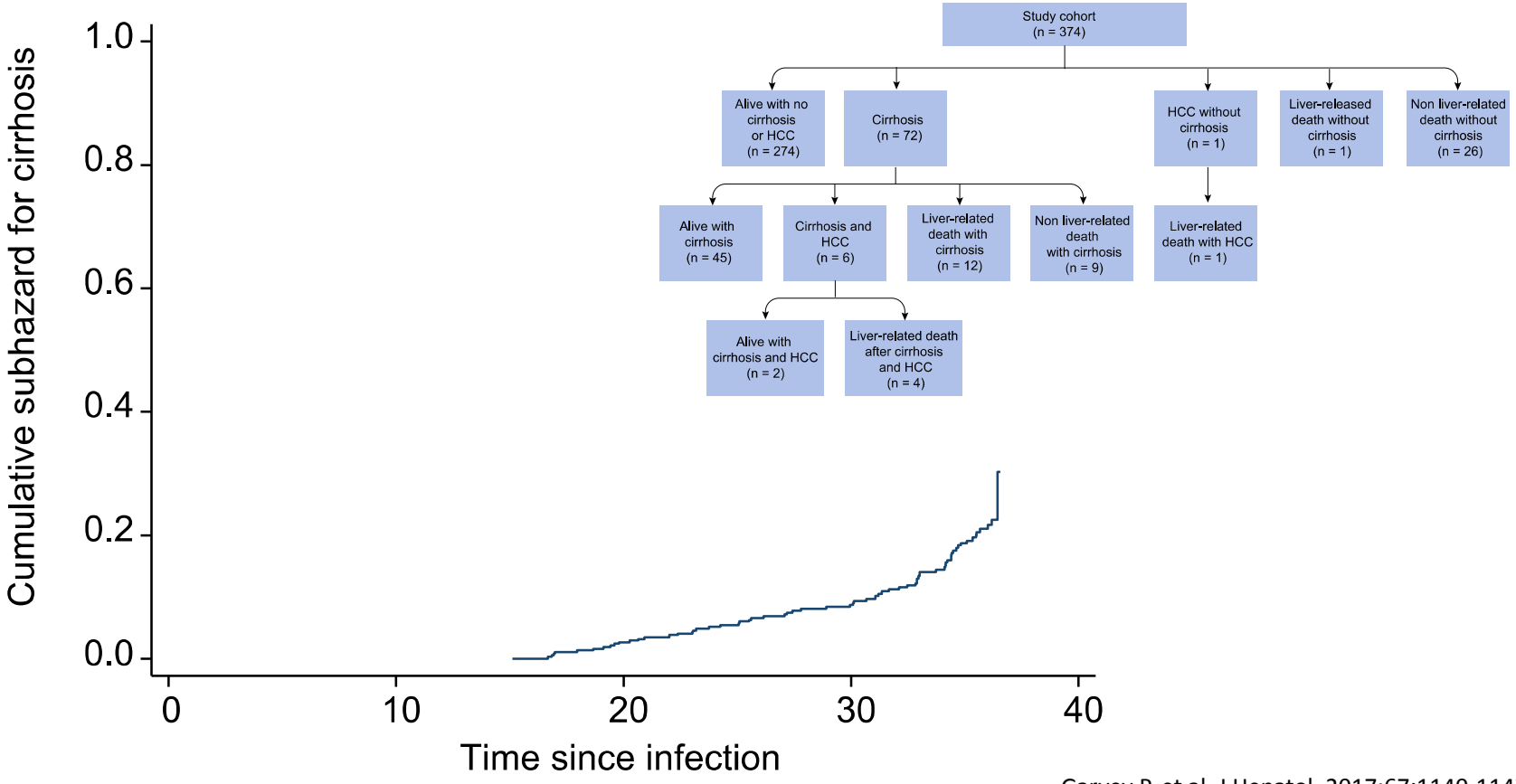
Στρογγυλό Τραπέζι με θέμα:

«*Χρονία Λοίμωξη με τον ιό της Ηπατίτιδας C:*
*Τρέχουσα εμπειρία και μέλλον****»***


23ο Ετήσιο Σεμινάριο Συνεχιζόμενης Ιατρικής Εκπαίδευσης Νοσοκομείου «Ο Ευαγγελισμός»
Αθήνα, 26 Φεβρουαρίου – 2 Μαρτίου 2018
Δεν υπάρχει σύγκρουση συμφερόντων με τις παρακάτω χορηγούς εταιρείες:
NOVARTIS, JANSSEN ONCOLOGY, ABBVIE, BRISTOL-MYERS SQUIBB, MEDTRONIC, TAKEDA, GENESIS, MSD, PFIZER, AMGEN, ASTELLAS, GILEAD, AENORASIS, BAXTER, BIANEΞ, WINMEDICA, ABBOTT, BIOΣΕΡ, SANOFI, ANGELINI, DEMO, ELPEN, EDWARDS, ROCHE, RONTIS, SPECIFAR, UCB, ΥΓΕΙΟΔΥΝΑΜΙΚΗ, MAVROGENIS

Outcomes in women infected by HCV-contaminated anti-D immunog. during 1970s

N=682♀



Garvey P, et al. J Hepatol. 2017;67:1140-1147

Στόχοι της θεραπείας στην ΧΗC

Βελτίωση της επιβίωσης

Κύριος στόχος

Η επίτευξη μακροχρόνιας ιολογικής απόκρισης (SVR)

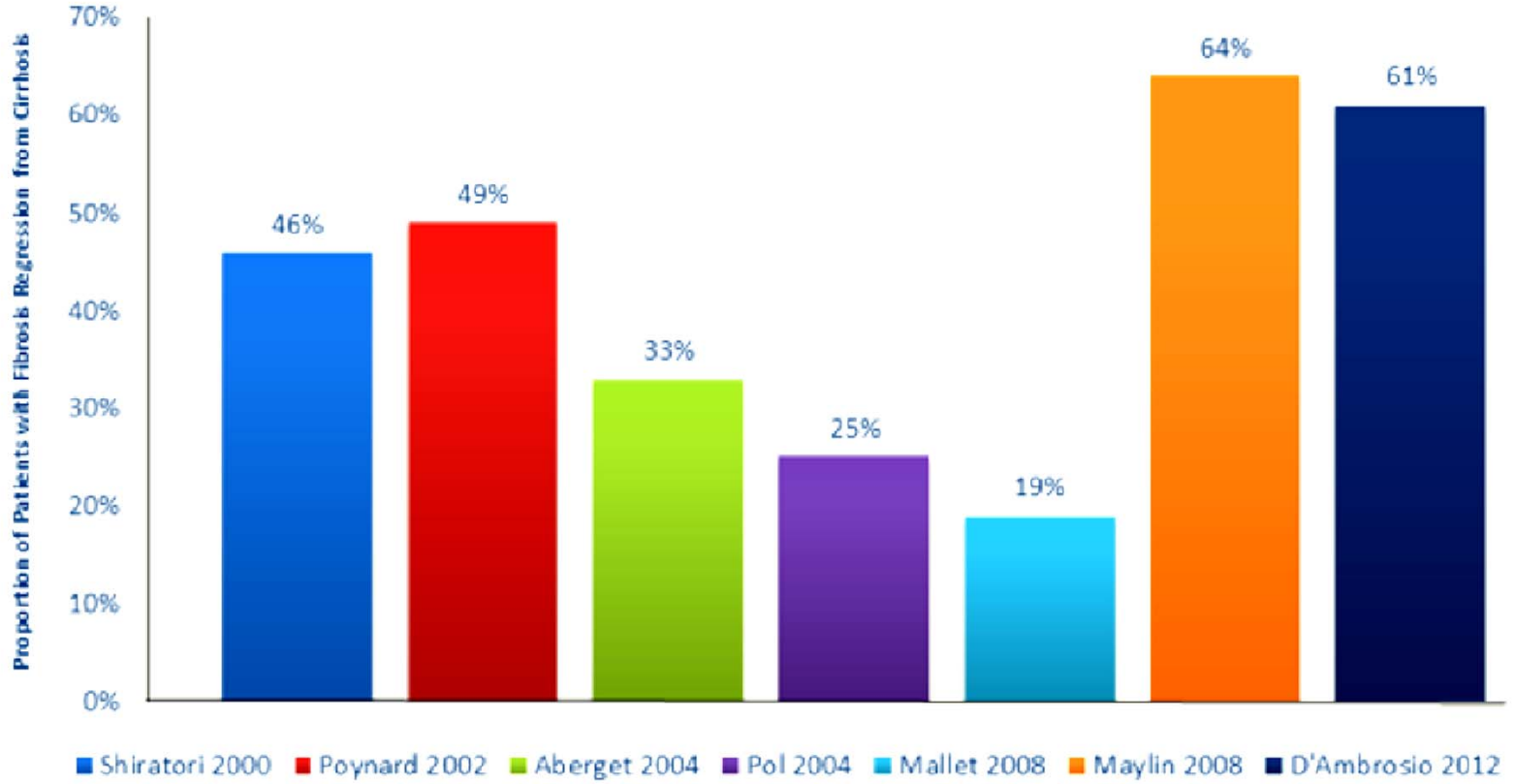
Μείωση κινδύνου ανάπτυξης ΗΚΚ

Ιστολογική βελτίωση

Υποστροφή της ίνωσης/κίρρωσης

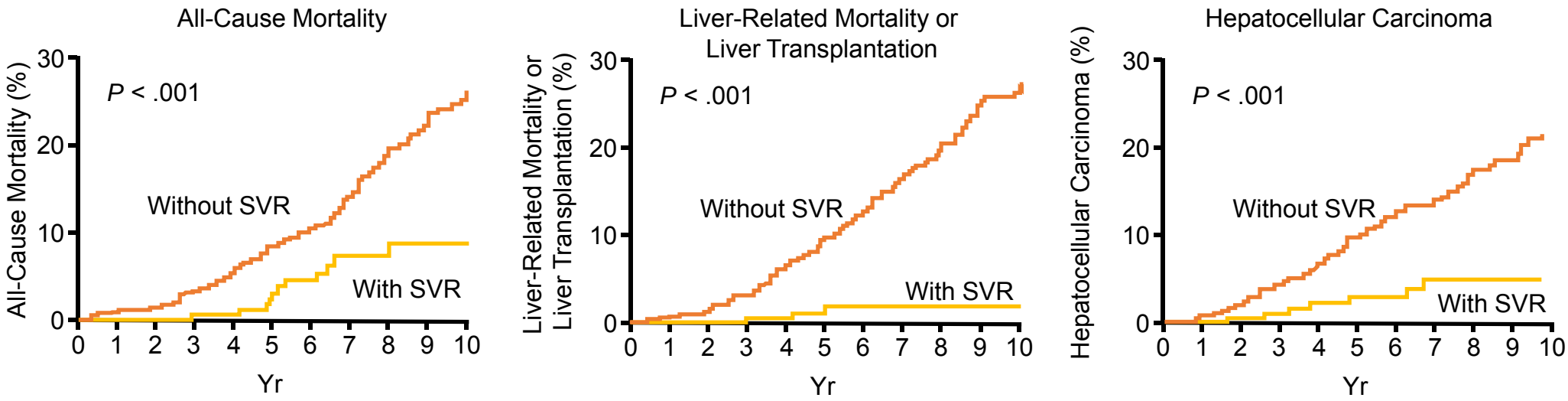
Αναστολή της εξέλιξης της ηπατικής νόσου

Regression of fibrosis in patients with cirrhosis with paired liver biopsies after SVR



D'Ambrosio R, et al. Hepatology. 2012;56(2):532-43, Mallet V, et al. Ann Intern Med. 2008;149(6):399-403, Manns MP, et al. J Viral Hepat. 2013;20(8):524-9, Maylin S, et al. Gastroenterology 2008;135(3):821-9, Pol S, et al. Hum Pathol 2004;35:107-112, Poynard T, et al, Gastroenterology 2002;122:1303-1313, Shiratori Y, et al. Ann Intern Med 2000;132:517-524.

Hepatitis C virologic cure associated with improved outcomes



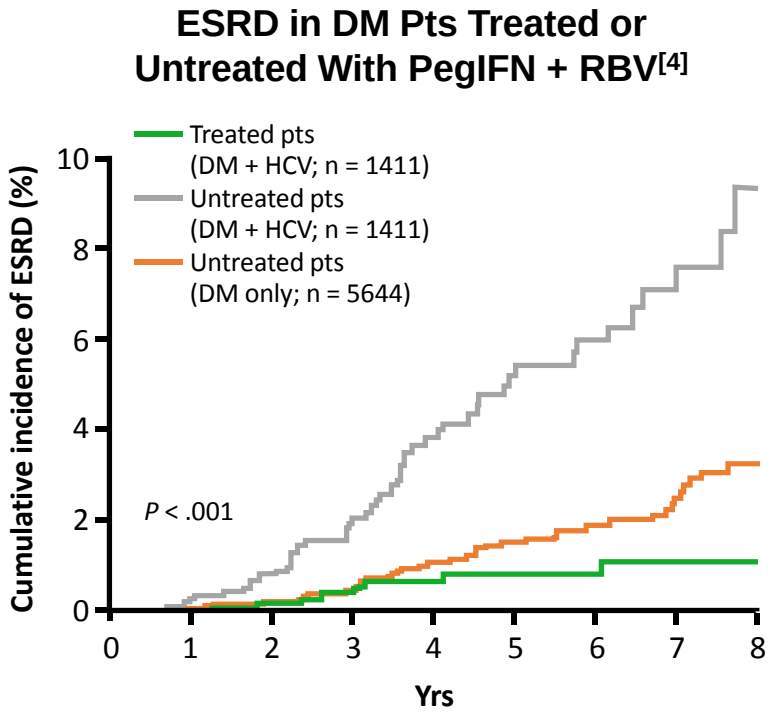
HR: 0.26 (95% CI: 0.14-0.49; *P* < .001)

- Virologic cure does not protect against reinfection

van der Meer AJ, et al. JAMA. 2012;308:2584-2593.

Benefits of HCV Therapy Extend Beyond the Liver: Diabetes

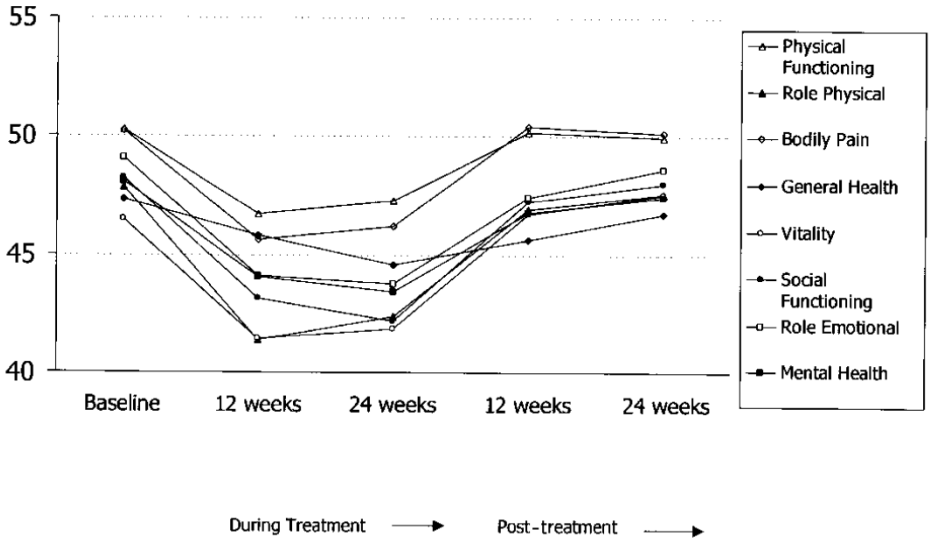
- HCV cure significantly reduces incidence of type 2 DM[1]
  - HCV pts have 2-3 x greater odds of DM[2]
- SVR may prevent and improve IR[3]
  - IR and DM increase risk and rate of fibrosis[2]
- PegIFN + RBV associated with improved renal/cardiovascular outcomes in pts with DM + HCV[4]

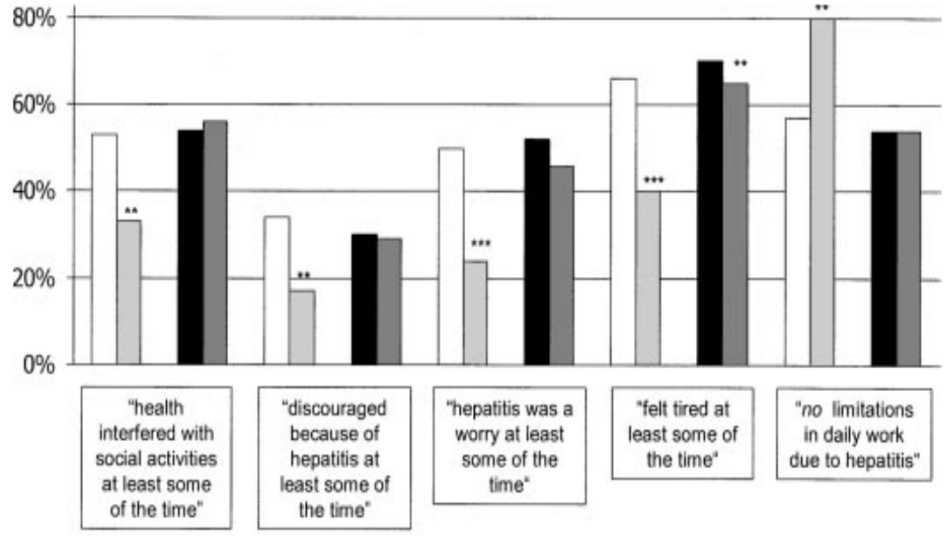


1. Arase Y, et al. Hepatology. 2009;49:739-744. 2. Brandman D, et al. Diabetes Care. 2012;35:1090-1094. 3. Aghemo A, et al. Hepatology. 2012;56:1691-1687.4. Hsu YC, et al. Hepatology. 2014;59:1293-1302.

SVR improved quality of life

324 patients with CHC who had responded to interferon treatment but relapsed

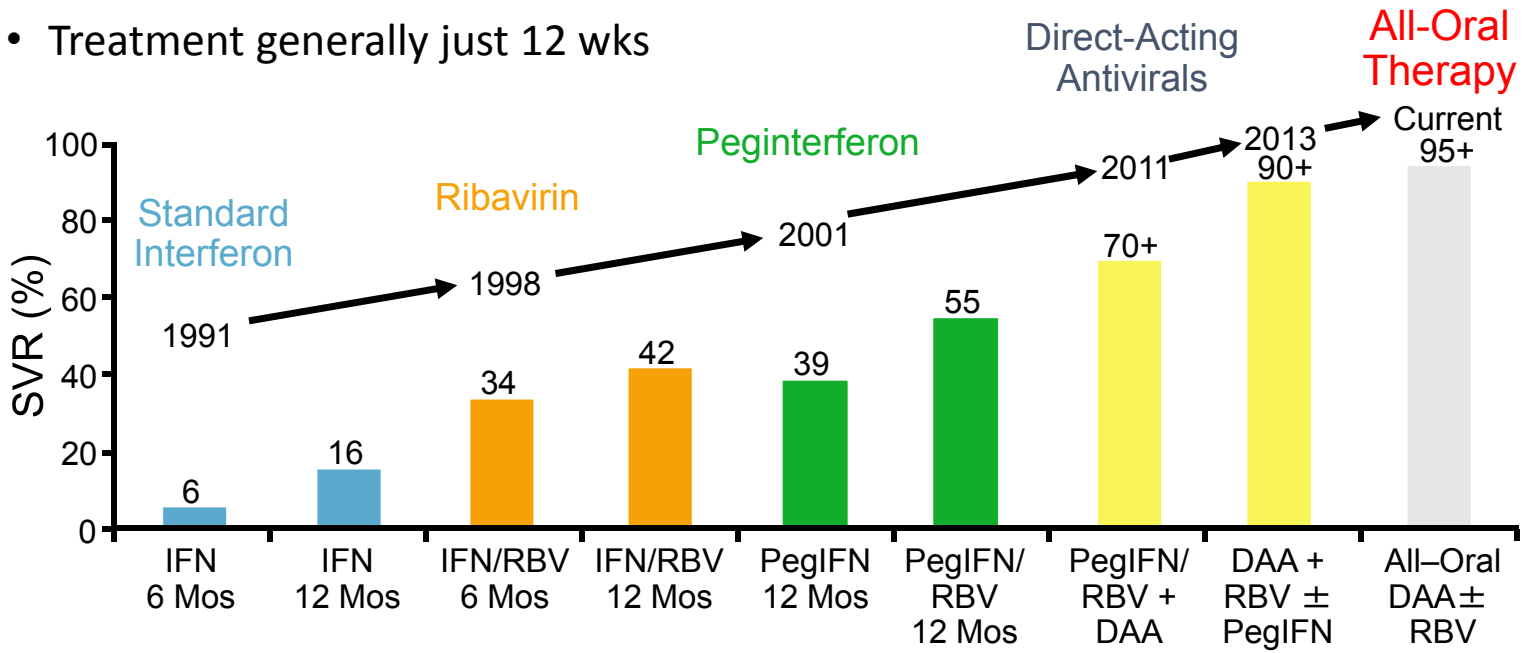




Ware JJ, et al. Hepatology 1999;30:550–555.

Nearly everyone with HCV can now be treated successfully

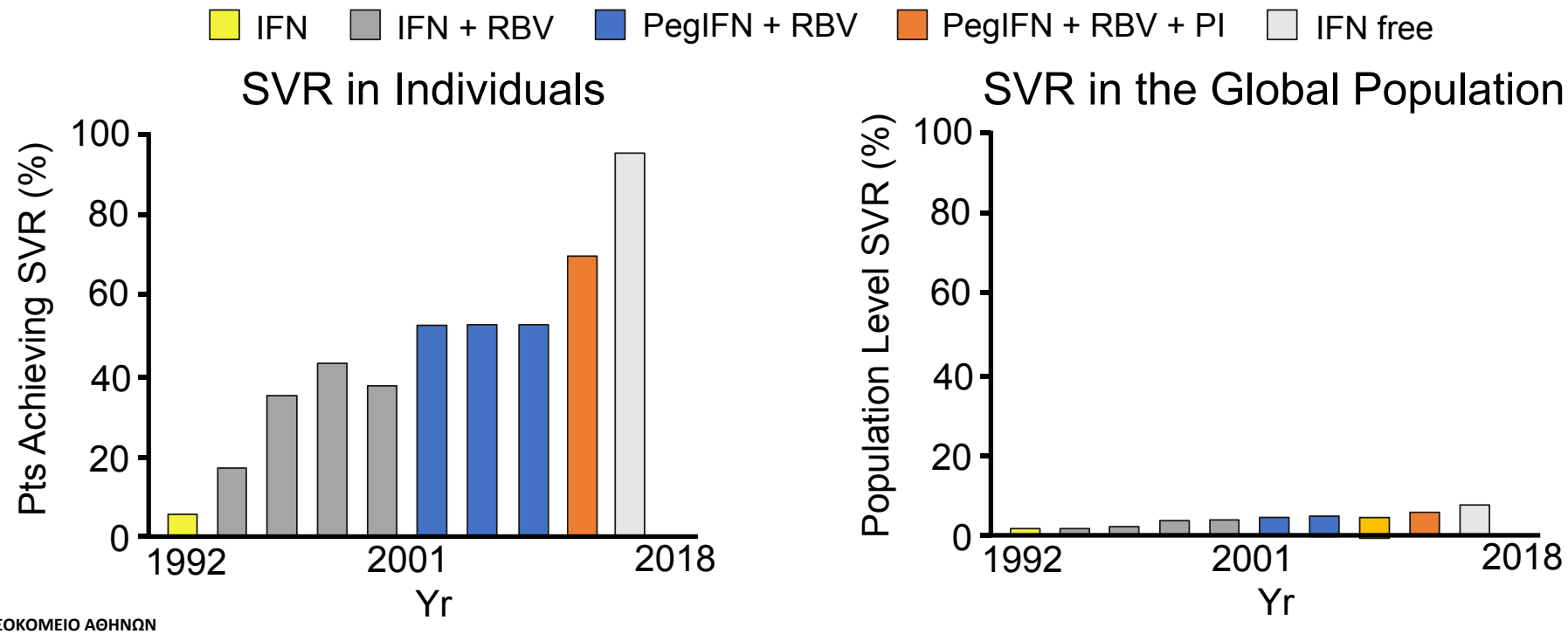
- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks



Manns MP, et al. Lancet. 2001;358:958-965, Fried MW, et al. N Engl J Med. 2002;347:975-982, Poordad F, et al. N Engl J Med. 2011;364:1195-1206, Jacobson IM, et al. N Engl J Med. 2011;364:2405-2416, Lawitz E, et al. N Engl J Med. 2013;368:1878-1887, Afdhal N, et al. N Engl J Med. 2014;370:1889-1898, Ferenci P, et al. N Engl J Med. 2014;370:1983-1992, Feld JJ, et al. N Engl J Med. 2014;370:1594-1603, Kwo P, et al. EASL 2015. Abstract LB14, Zeuzem S, et al. Ann Intern Med. 2015;163:1-13, Feld JJ, et al. N Engl J Med. 2015;373:2599-2607, Foster GR, et al. N Engl J Med. 2015;373:2608-2617.

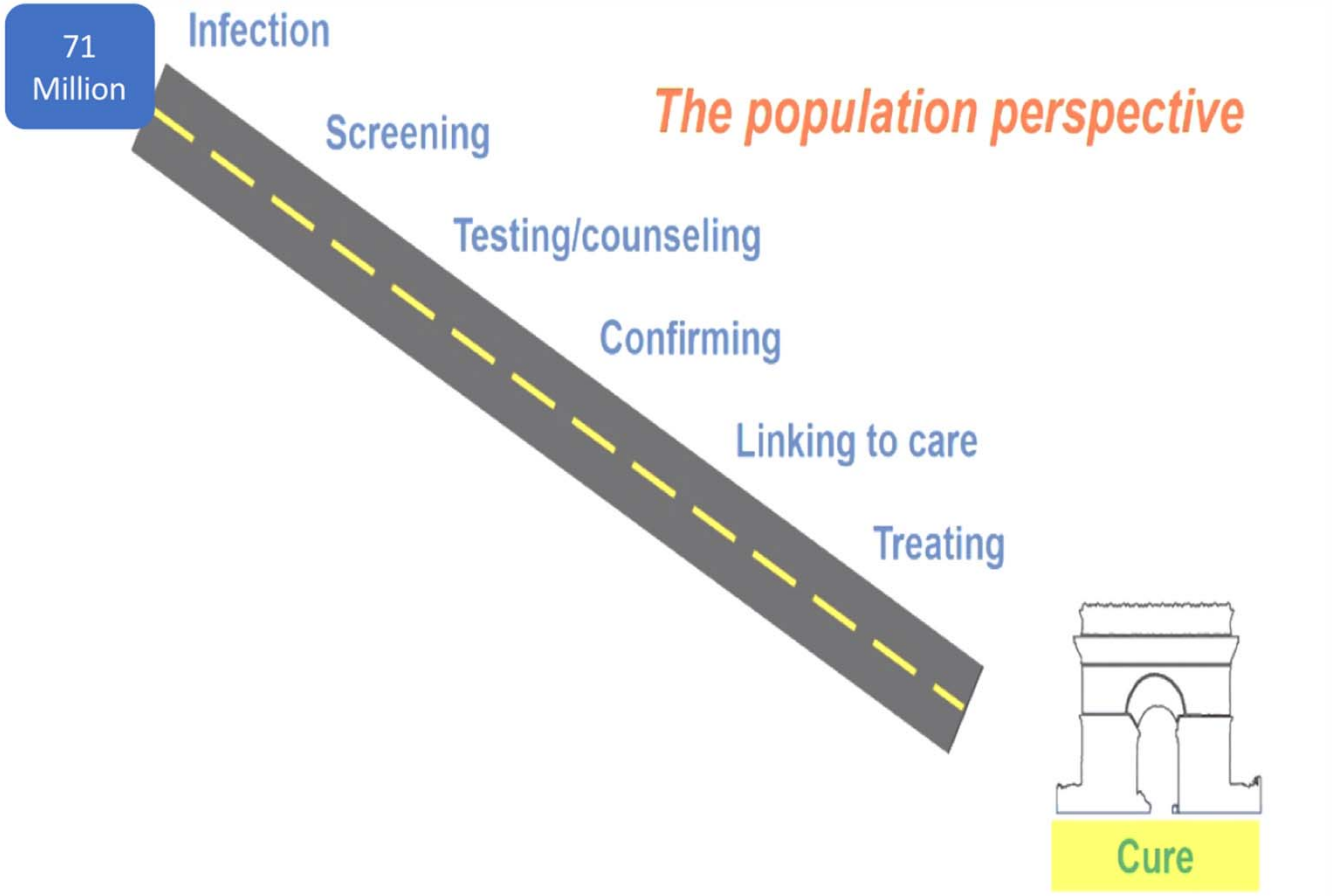
HCV is curable in > 95% of pts with DAA therapy

- Curing the individual is now easy; curing the population will take a lot more work . . .



Thomas DL, et al. Antivir Ther. 2012;17:1183-1188.

Ο δρόμος προς την θεραπεία της HCV λοίμωξης



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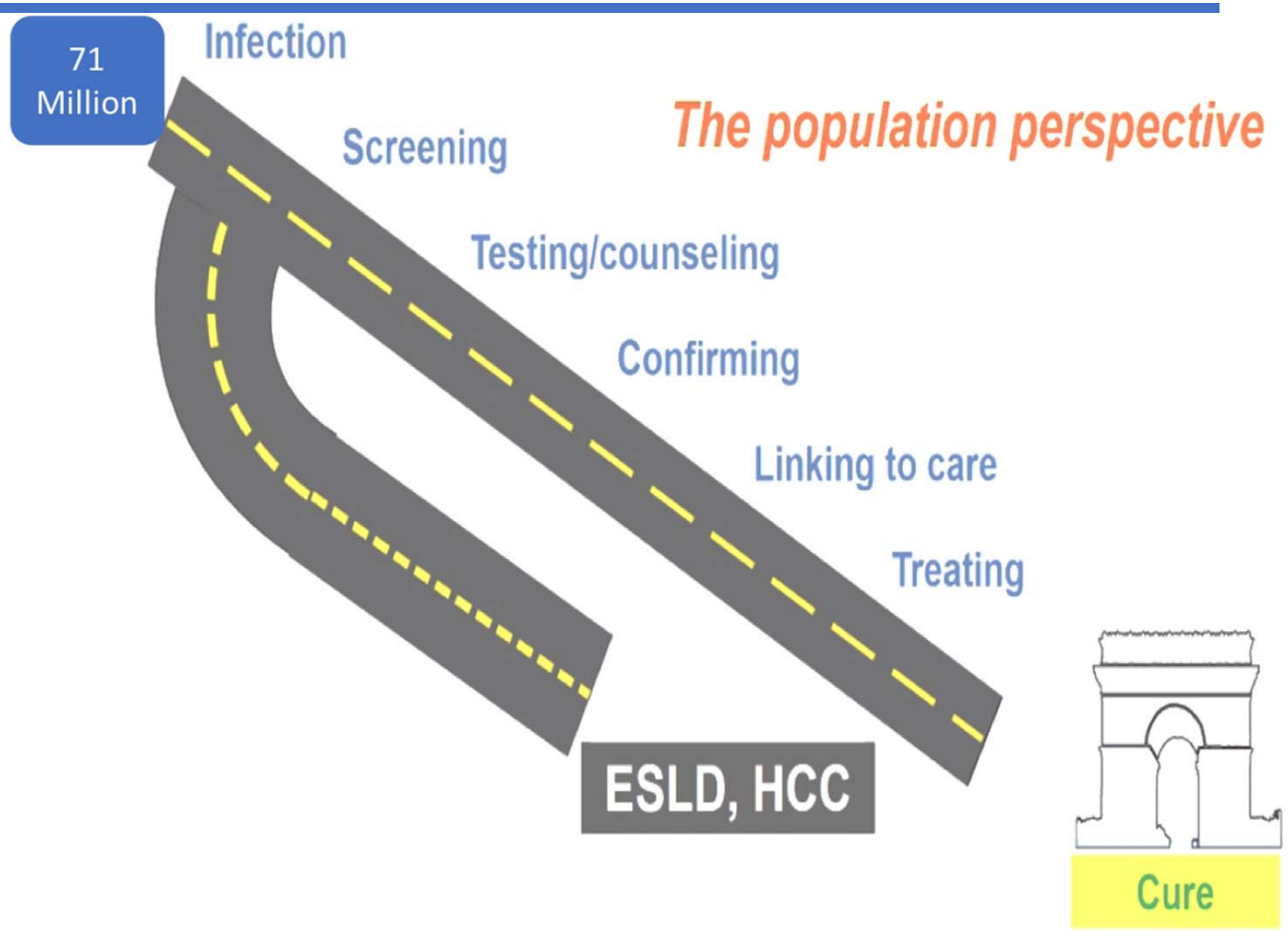
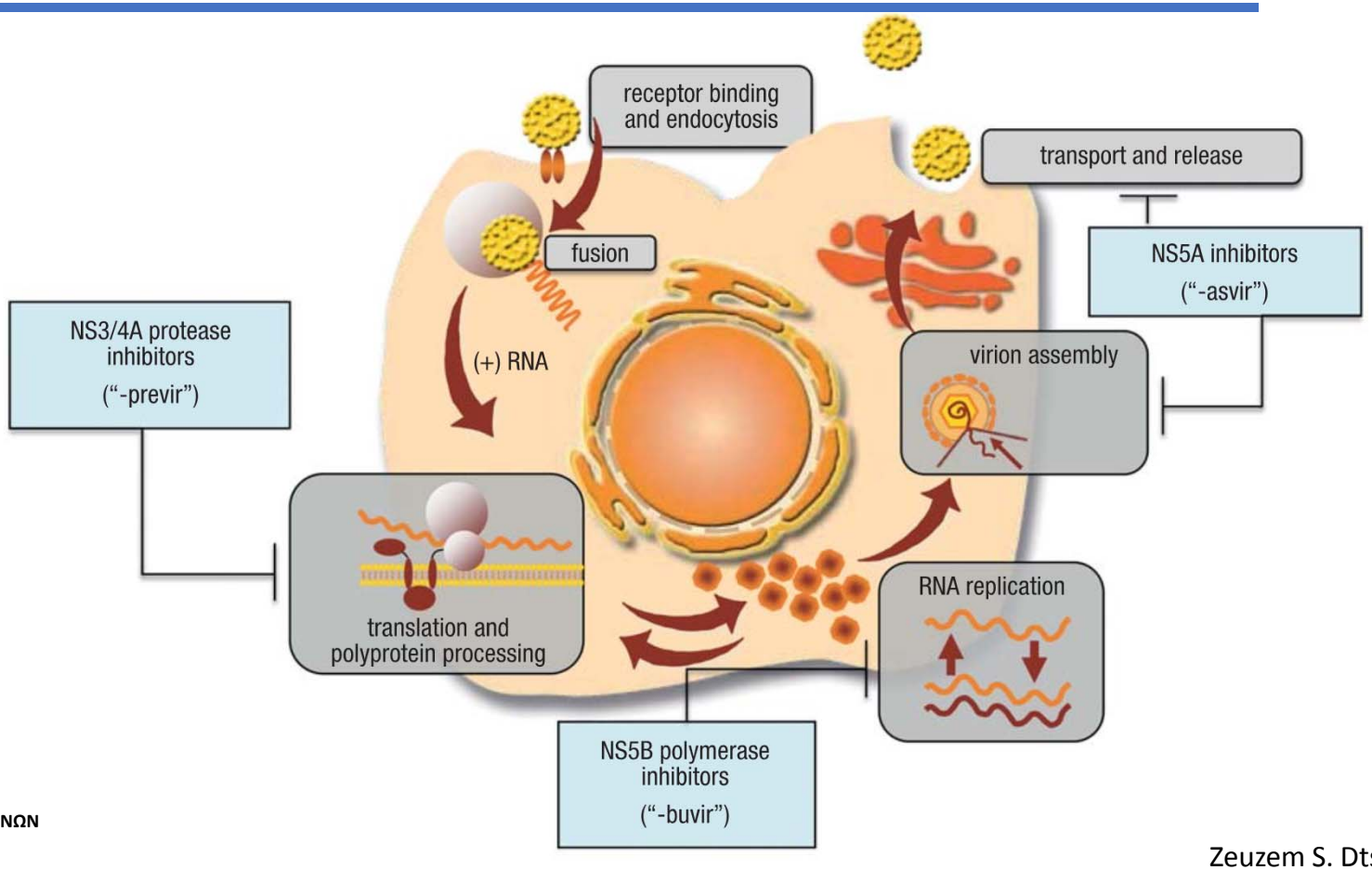


Replication cycle of HCV and mechanisms of action of anti-HCV drugs



Zeuzem S. Dtsch Arztebl Int. 2017;114:11-21.

Overview of IFN-Free treatment regimens recommended

	SOF + RBV	LDV/SOF ± RBV	SOF/VEL ± RBV	OMV/PTV/ RTV + DSV ± RBV	OMV/PTV/ RTV ± RBV	GRZ/EBV ± RBV	SOF + DCV ± RBV	SOF + SMV ± RBV
GT 1	✗	✓	✓	✓	✗	✓	✓	Suboptimal
GT 2	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT 3	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT 4	✗	✓	✓	✗	✓	✓	✓	✓
GT 5	✗	✓	✓	✗	✗	✗	✓	✗
GT 6	✗	✓	✓	✗	✗	✗	✓	✗

SOF + DCV ± RBV is not approved in the EU for GT 2, GT 5 or GT 6 patients.
Regimens not included in the SmPC posology table (Table 1) are shown in grey

EASL CPGs J Hepatol. 2017;68:153-194.

Genotyping activity of HCV drugs

	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
Paritaprevir/r + Ombitasvir ± Dasabuvir ± RBV	x			x		
Grazoprevir + Elbasvir	x			x		(x)
Glecaprevir + Pibrentasvir	x	x	x	x	x	x

EASL CPGs J Hepatol. 2017;68:153-194.

Rates of SVR >95% are considered a “must have” in the new era

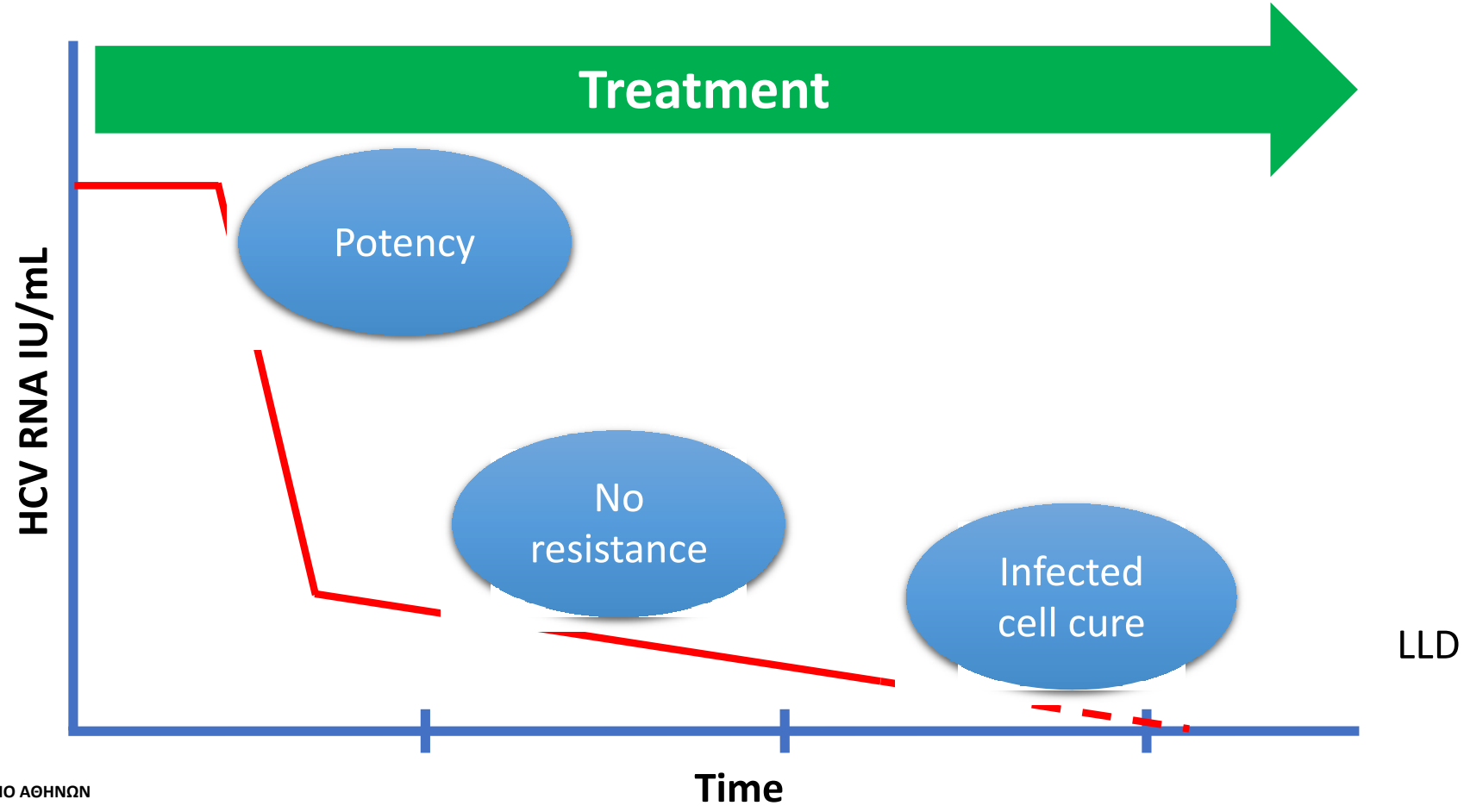
Summary of Phase 3 studies of IFN-free therapy in GT 1 patients published in NEJM in 2014

Trial	Regimen
ION-1	LDV/SOF ± RBV
ION-1	LDV/SOF ± RBV
ION-1	LDV/SOF ± RBV
SAPPHIRE-I	OMV/PTV/RTV + DSV + RBV
SAPPHIRE-II	OMV/PTV/RTV + DSV + RBV
PEARL-III	OMV/PTV/RTV + DSV ± RBV
PEARL-IV	OMV/PTV/RTV + DSV ± RBV
TURQUOISE-II	OMV/PTV/RTV + DSV + RBV

Short, well-tolerated treatment regimens
Included treatment-naïve and -experienced patients +/- cirrhosis

Liang JT, & Ghany MG. N Engl J Med 2014; 370:2043-2047

Concepts in HCV therapy



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Sofosbuvir + Velpatasvir	x	x	x	x	x	x
Grazoprevir + Elbasvir	x			x		(x)
Glecaprevir + Pibrentasvir	x	x	x	x	x	x

EASL CPGs J Hepatol. 2017;68:153-194.

SmPC: Glecaprevir + Pibretasvir (Maviret®)

(1) Recommended Maviret treatment duration for patients without prior HCV therapy

Genotype	Recommended treatment duration	
	No cirrhosis	Cirrhosis
All HCV genotypes	8 weeks	12 weeks

(2) Recommended Maviret treatment duration for patients who failed prior therapy with peg-IFN + ribavirin +/- sofosbuvir, or sofosbuvir + ribavirin

Genotype	Recommended treatment duration	
	No cirrhosis	Cirrhosis
GT 1, 2, 4-6	8 weeks	12 weeks
GT 3	16 weeks	16 weeks

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004430/WC500233677.pdf; January 2018

Comparison of pangenotypic regimen

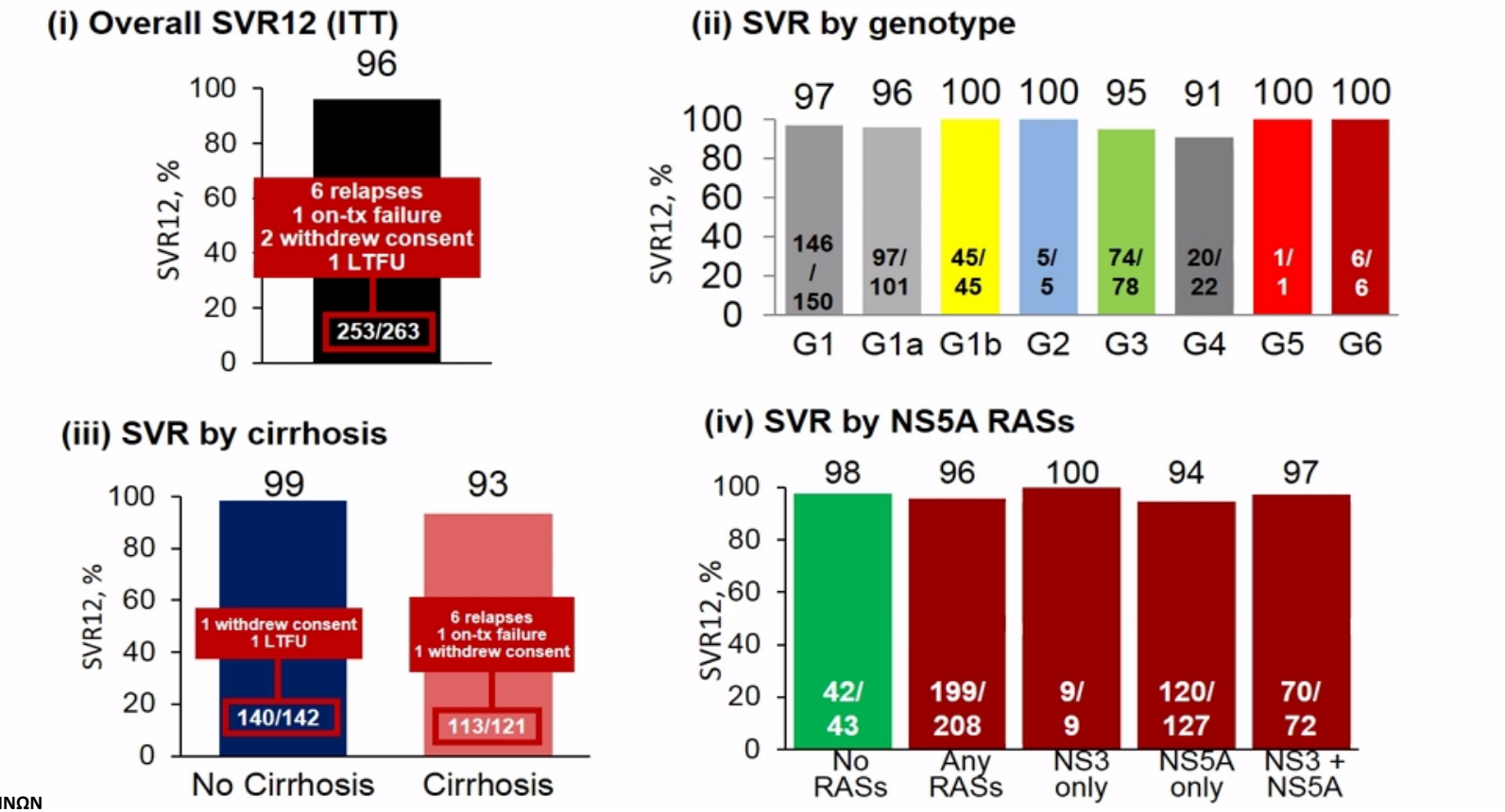
Sofosbuvir + Velpatasvir

- ✓ Same treatment duration independent of fibrosis stage (12 weeks)
- ✓ Decompensated cirrhosis
- ✓ CrCl > 30 ml/min
- ✓ RBV in GT3 patients with cirrhosis and all patients with decompensated cirrhosis

Grecaprevir + Pibrentasvir

- ✓ 8-week treatment duration in patients without cirrhosis
- ✓ Treatment in all CKD stages, but not in patients with decompensated cirrhosis
- ✓ No RBV in GT3 with cirrhosis, but treatment prolongation to 16 weeks in treatment-experienced patients with or without cirrhosis

SOF/VEL/VOX for 12 weeks as salvage regimen in NS5A inhibitor- experienced GT 1-6 patients



Bourlière M, et al. N Engl J Med 2017; 376:2134-2146.

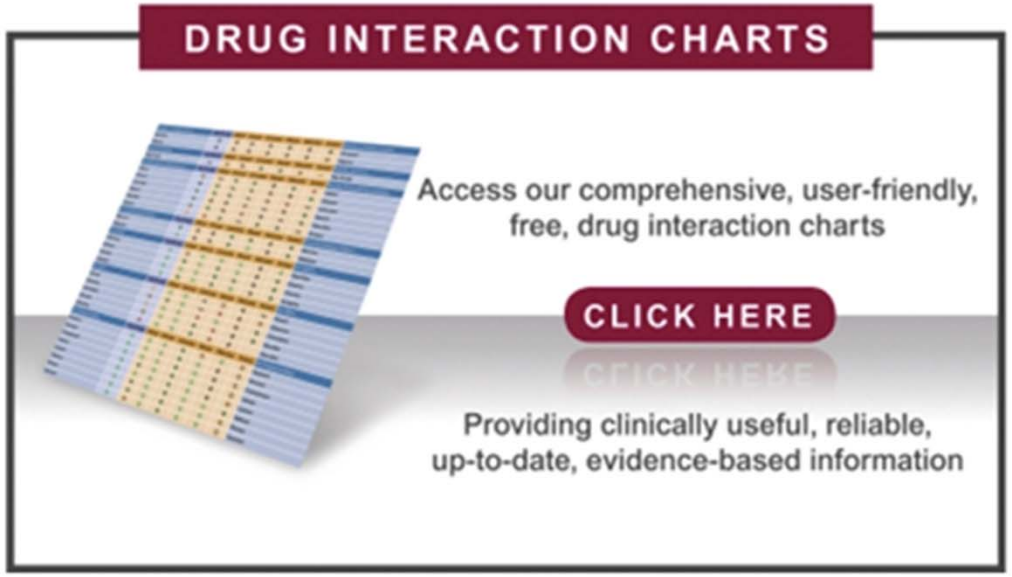
Safety profiles of DAAs

Very common (≥1/10) AEs reported in SmPCs	
SOF + RBV	Blood bilirubin increased, haemoglobin decreased, fatigue, headache, insomnia, irritability, nausea
SOF + SMV	Rash,
SOF + DCV	Fatigue, headache
LDV/SOF	Fatigue, headache
OMV/PTV/RTV + DSV + RBV	Asthenia, fatigue, insomnia, nausea, pruritus
EBR/GZR	Fatigue, headache
SOF/VEL	Fatigue, headache, nausea

Janssen-Cilag Ltd. OLYSIO▼ (simeprevir) SmPC, August 2016; Bristol-Myers Squibb Pharma EEIG. DAKLINZA▼ (daclatasvir) SmPC, July 2016; Gilead Sciences Europe Ltd. SOVALDI▼ (sofosbuvir) SmPC, March 2016; Gilead Sciences Europe Ltd. HARVONI▼ (ledipasvir/sofosbuvir) SmPC, July 2016; AbbVie Ltd. VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir) SmPC, August 2016; AbbVie Ltd. EXVIERA▼ (dasabuvir) SmPC, May 2016; Gilead Sciences Europe Ltd. EPCLUSA▼ (velpatasvir/sofosbuvir) SmPC, July 2016; Merck Sharp & Dohme Ltd. ZEPATIER▼ (elbasvir/grazoprevir) SmPC, July 2016

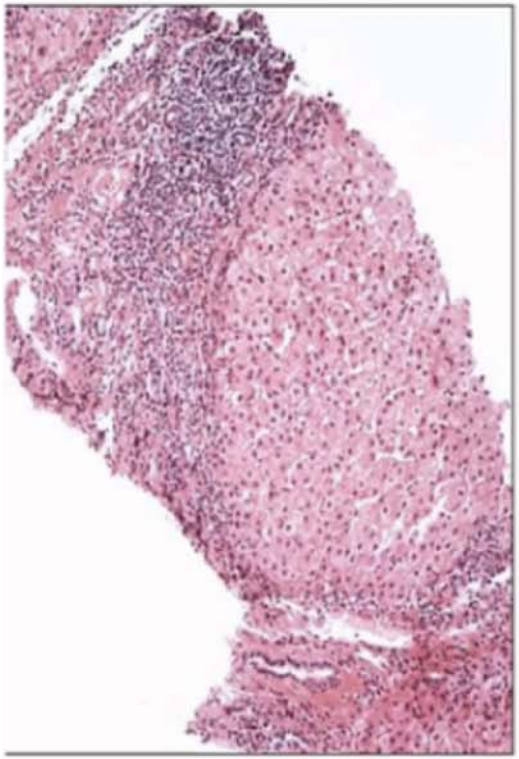
Drug-Drug Interactions
www.hep-druginteractios.org

UNIVERSITY OF LIVERPOOL

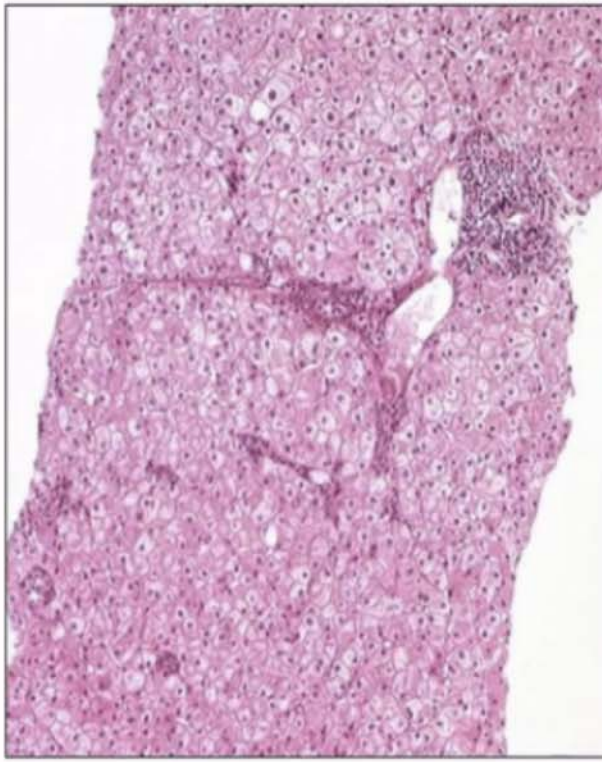


Cirrhosis regression after antiviral treatment

Before treatment
HCV cirrhosis

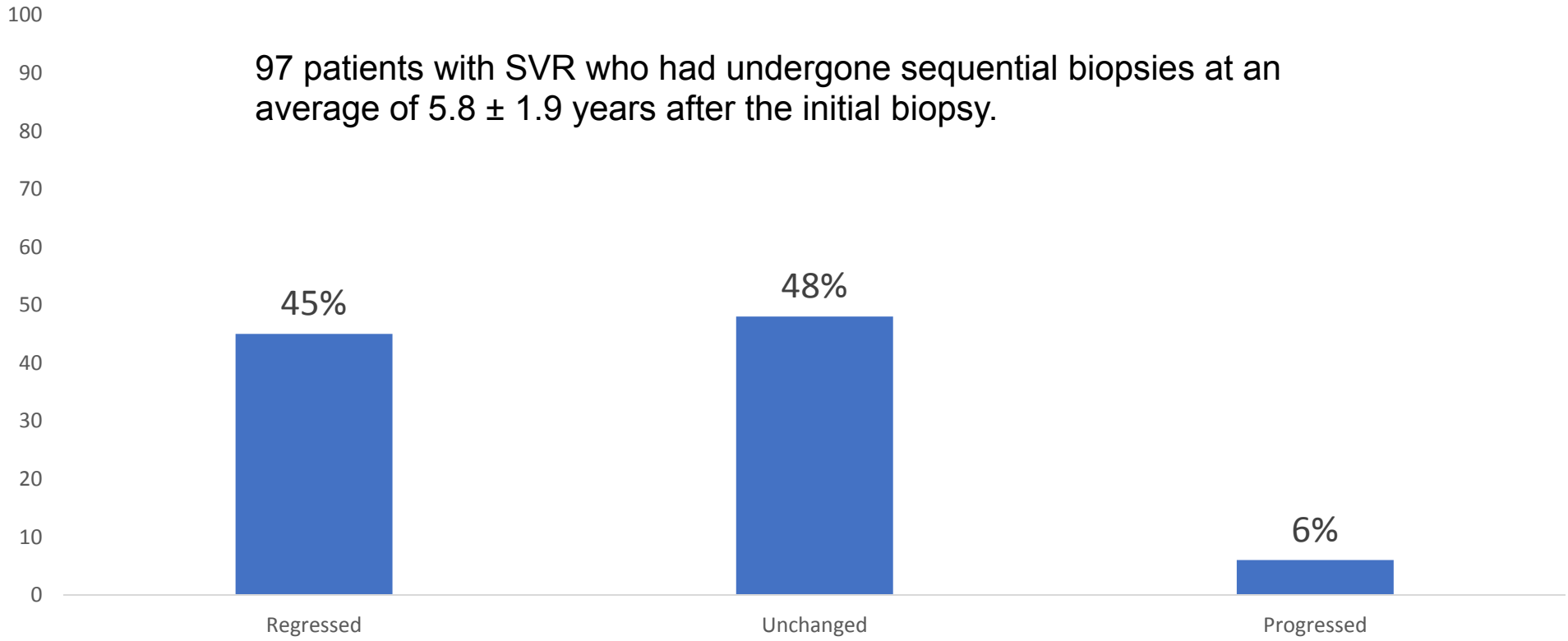


6 years AFTER SVR
«normal» organisation



D'Ambrosio R, et al. Hepatology 2012;56:532–543.

But a small proportion shows progression



Tachi Y, et al. Hepatol Res 2015;45:238–246.

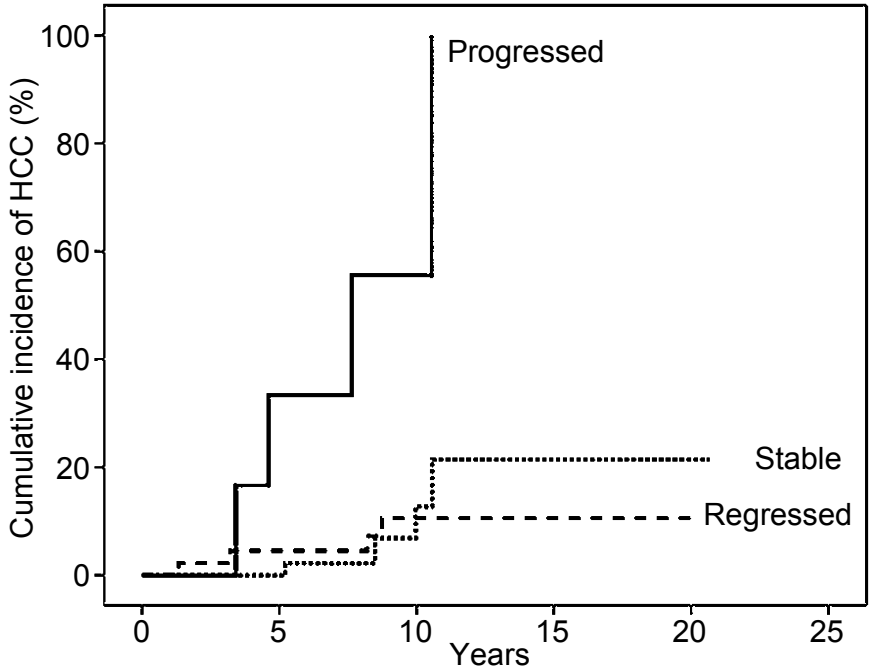
Factors most consistently linked with regression

- Lower stages of fibrosis at the time of SVR.
- Younger age (<40 years).
- Female gender.
- Body mass index (BMI)<27 kg/m^2.

Poynard T, et al. Gastroenterology 2002;122:1303–1313.

Fibrosis changes and HCC incidence

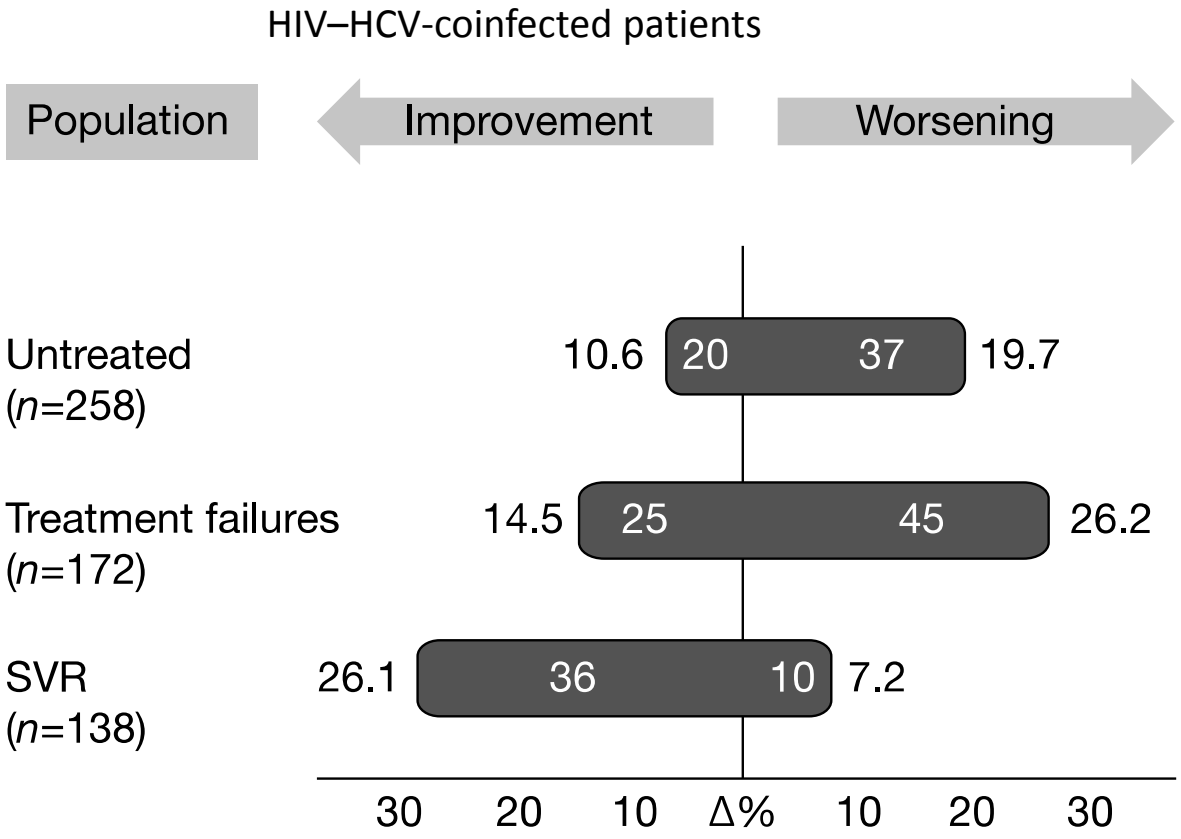
97 patients with SVR who had undergone sequential biopsies at an average of 5.8 ± 1.9 years after the initial biopsy.



Patients at risk	0 year	5 years	10 years	15 years	20 years
Regressed	44	42	18	2	1
stable	47	45	15	2	1
Progressed	6	3	1	0	0

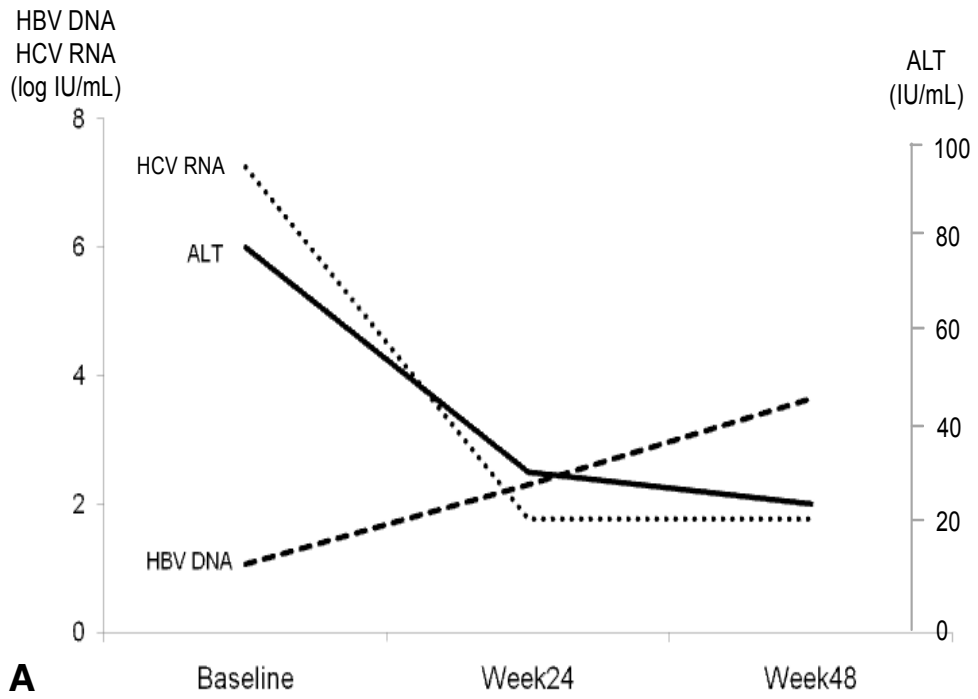
Tachi Y, et al. Hepatol Res 2015;45:238–246.

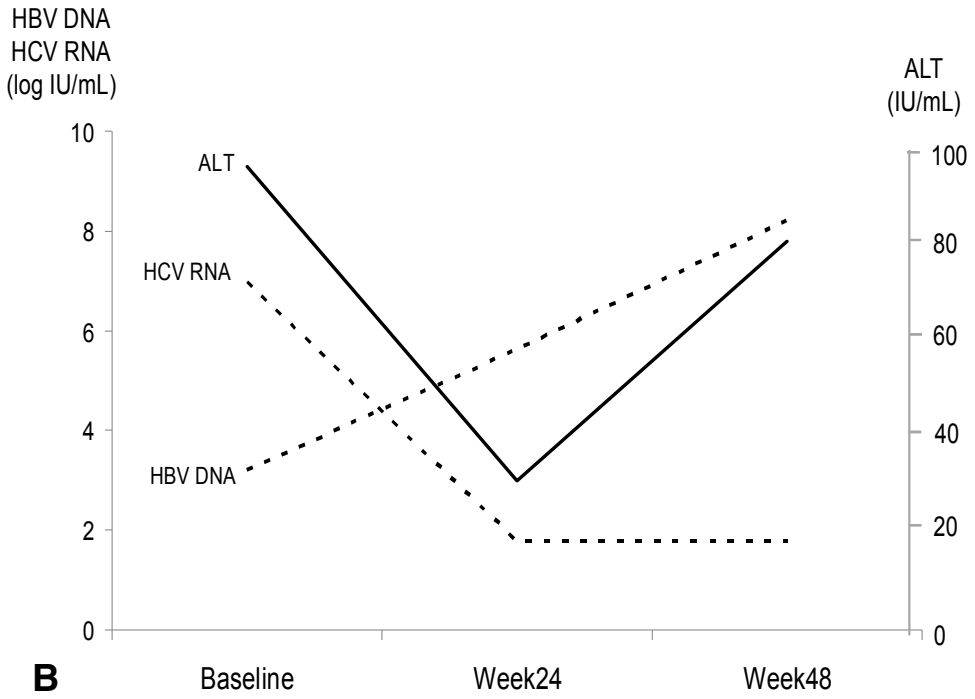
Controlling viral coinfections



Labarga P, et al. Antivir Ther 2015;20:329–334.

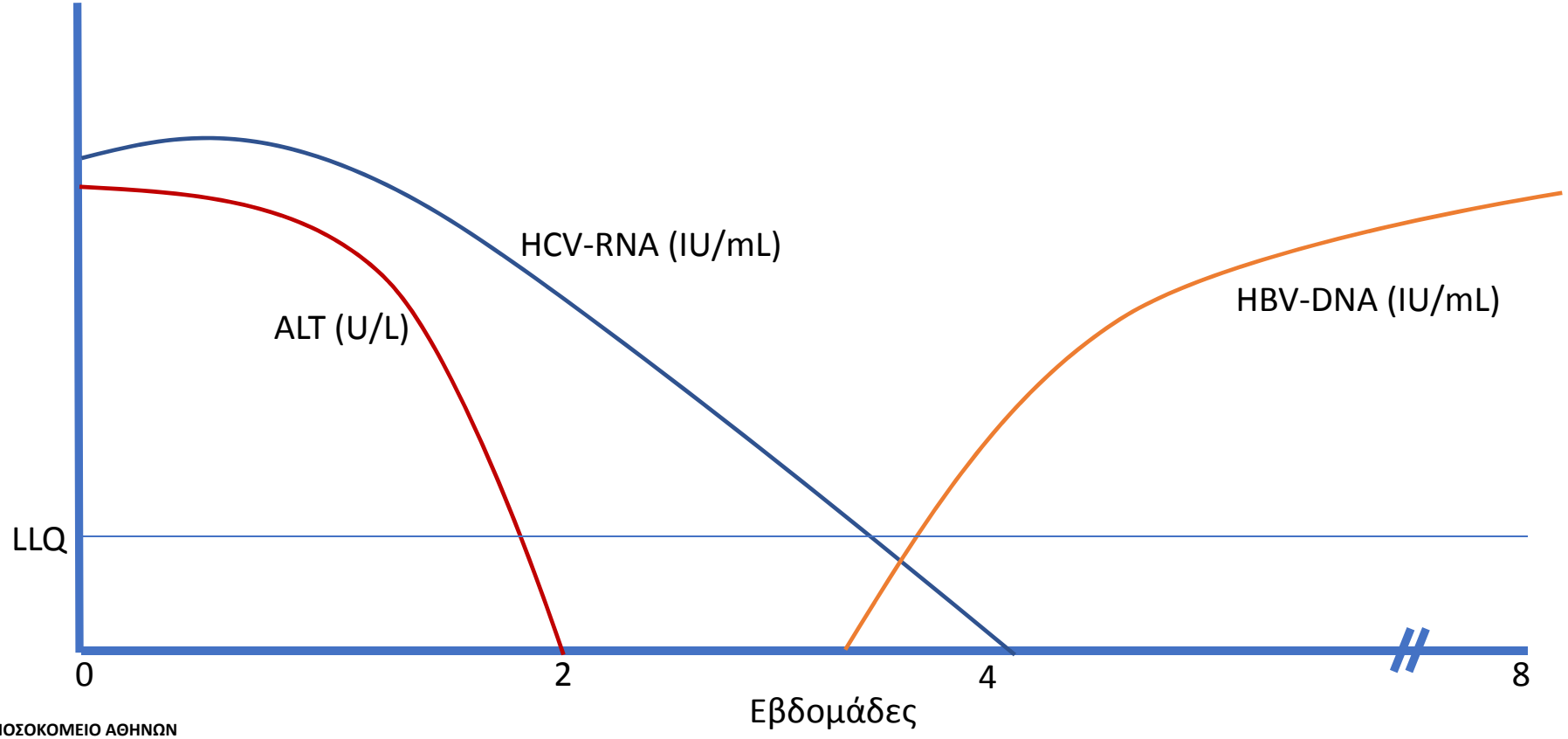
Maximize SVR benefits on fibrosis progression





Yu JW, et al. Liver Int 2009;29:1485–1493.

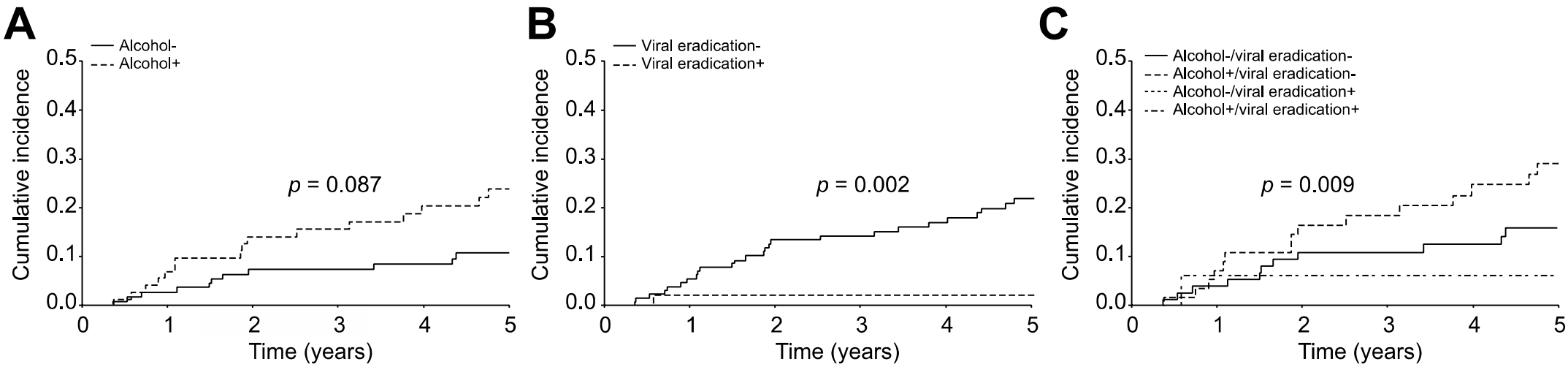
Φυσική ιστορία της επανενεργοποίησης του HBV κατά τη θεραπεία με DAAs



1. The Food and Drug Administration Adverse Event Reporting System (FAERS), 2. Balagopal A, Thio CL. Clin Infect Dis 2015;61:1307-9, 3. Collins JM, et al. Clin Infect Dis 2015;61:1304-6, 4. De Monte A, et al. J Clin Virol 2016;78:27-30, 5. Ende AR, et al. J Med Case Rep 2015;9:164, 6. Kimura H, et al. Kanzo 2015;56:422-27, 7. Wang C, et al. Clin Gastroenterol Hepatol. 2016 Jul 5. [Epub ahead of print].

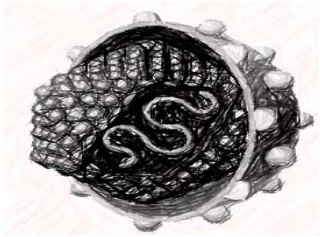
Alcohol intake increases the risk of HCC in hepatitis C virus-related compensated cirrhosis

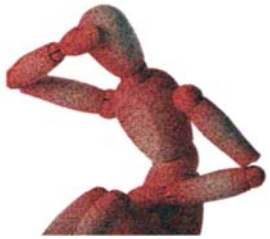
192 patients with compensated HCV-related cirrhosis, 74 patients consumed alcohol (median alcohol intake: 15 g/day); 68 reached viral eradication.



Vandenbulcke H, et al. J Hepatol 2016;65:543–551.

Hepatitis C and systemic inflammation





Systemic inflammation

HCV core protein

Other viral proteins

- Protein down-regulation of glucose transporter 2 (GLUT2)
- Down-regulation of the hepatic expression of both IRS-1 and IRS-2
- increase Ser(312) phosphorylation of the insulin receptor substrate-1

Elevated TNF-a levels

- IRS proteins function inhibition through phosphorylation by activated Ser/Thr kinases
- IR in muscle and liver through serum FFA increase by TNF-a inducted lipolysis
- TNF-a direct toxicity to b-cells causing IR
- TNF-a driven decrease of adiponectins

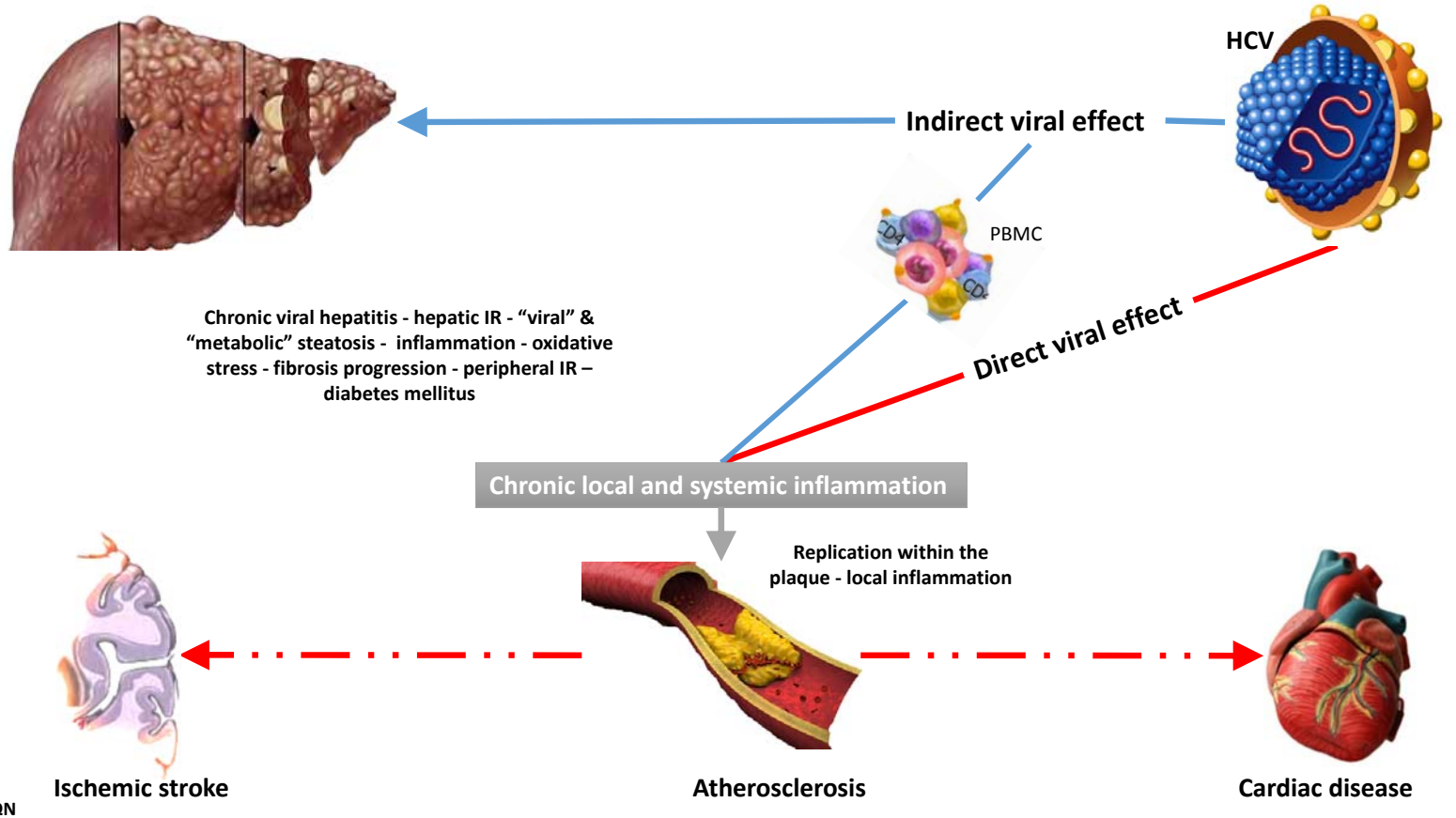
IL-6

- inhibition of hepatic insulin-dependent receptor auto-phosphorylation and IRS-1 tyrosine phosphorylation through induction of SOCS-3 protein

Insulin resistance (IR)

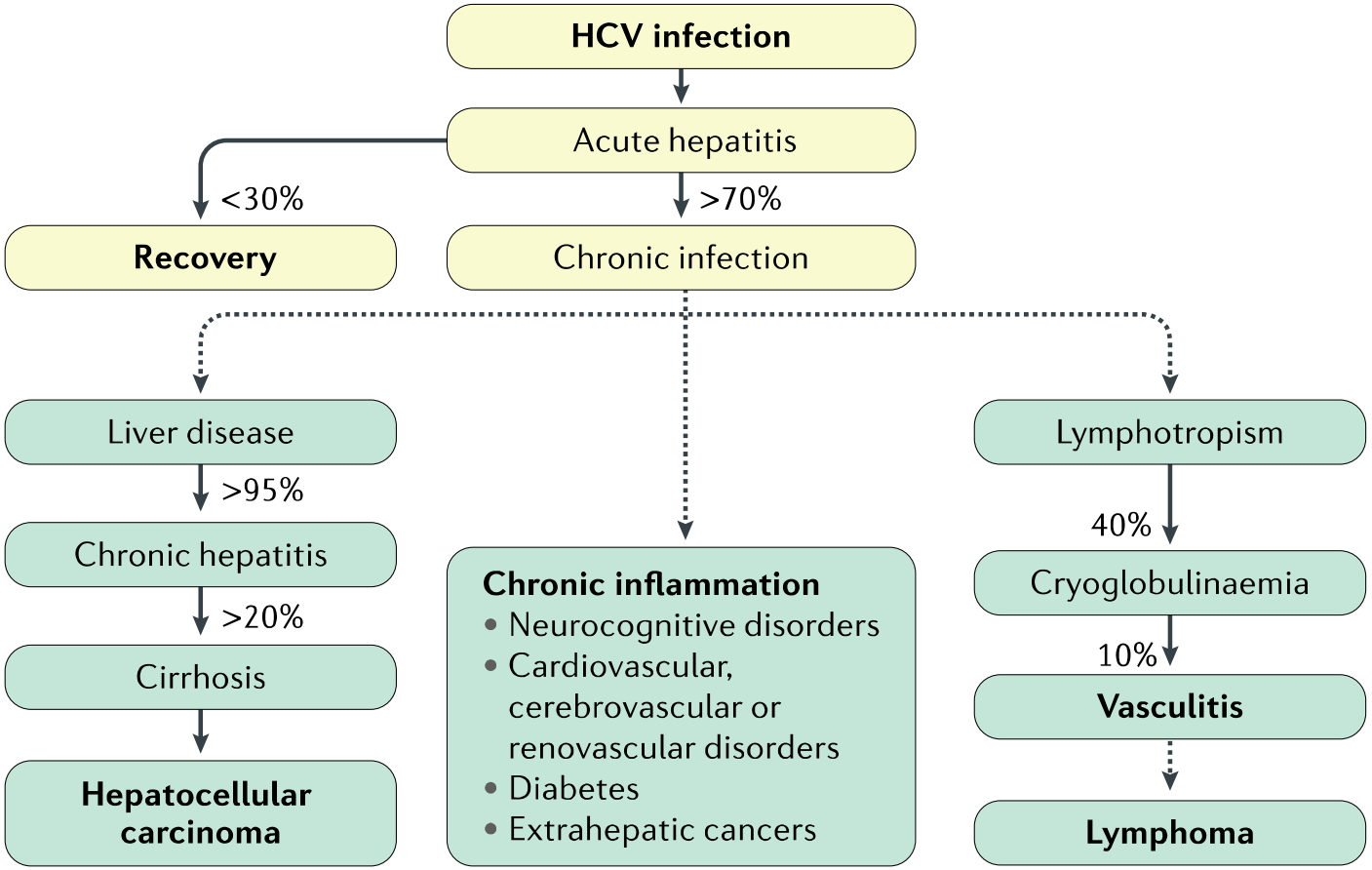
Voulgaris T, & Sevastianos VA. submitted.

Possible mechanisms connecting HCV infection and cardiovascular disease



Voulgaris T, & Sevastianos VA. Hepat Res Treat. 2016;2016:7629318.

The natural history of HCV infection



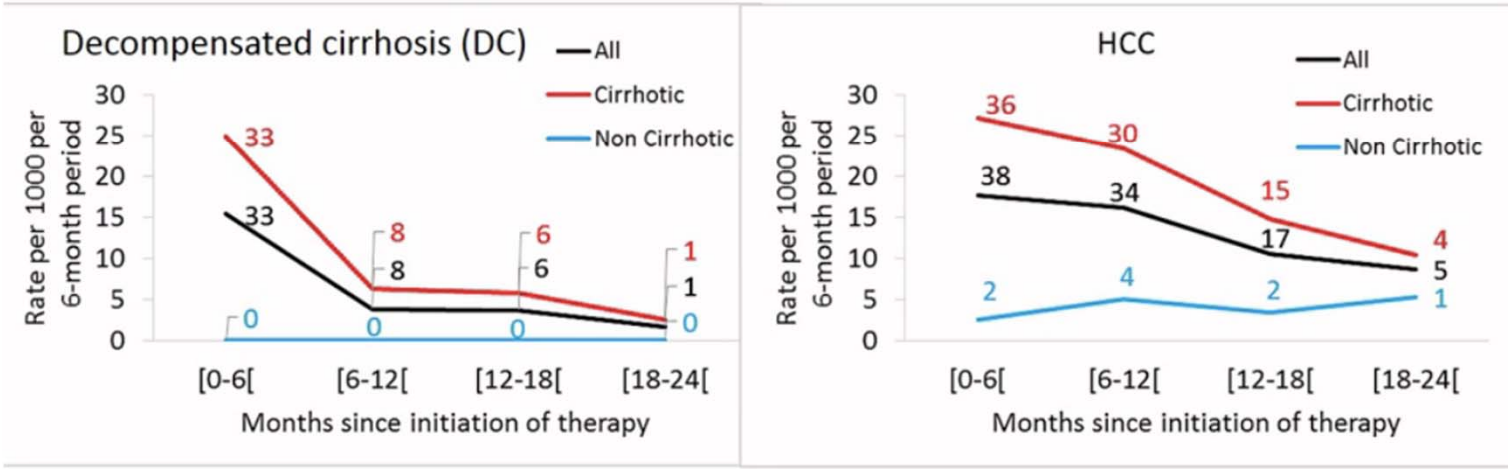
Pol S, et al. Nat Rev Gastroenterol Hepatol. 2018;[Epub ahead of print].

Can the use of DAA impact the HCV morbidity and mortality?

n=2,156 HCV-infected patients (63% cirrhotics) **without HCC or DC at inclusion**
Treated with DAA , SVR=90%

Median follow-up **18 (16-20) months**

Pol, S et al. ANRS-HEPATHER study group EASL 2016

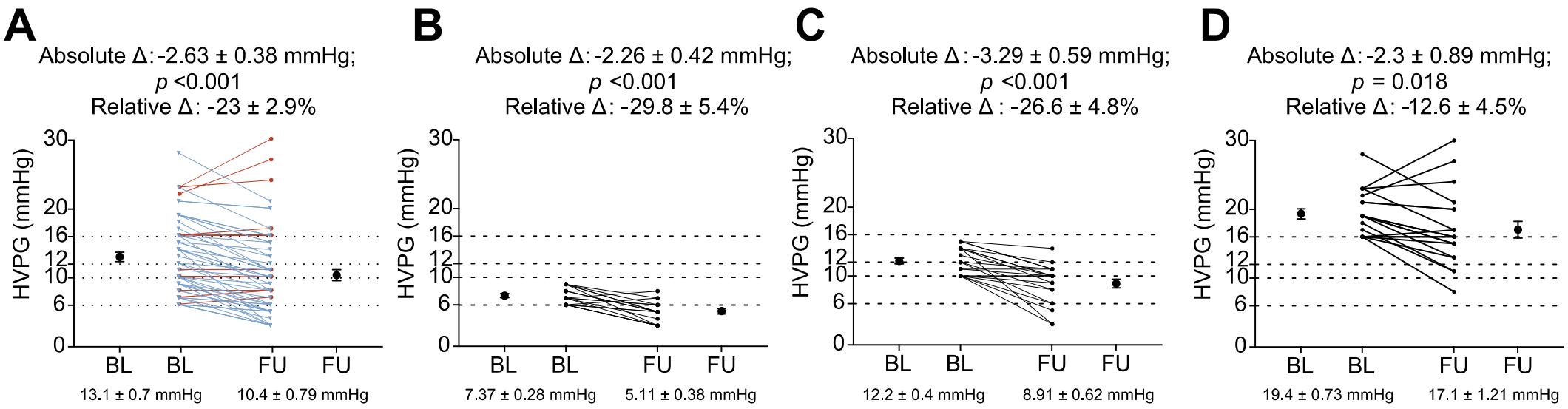


77% reduction in DC after 6 months (P<0.001)

44% reduction in HCC after 12 months (=0.025)

SVR to IFN-free therapies ameliorated HCV-induced portal hypertension

One hundred and four patients with portal hypertension (HVPG ≥6 mmHg)



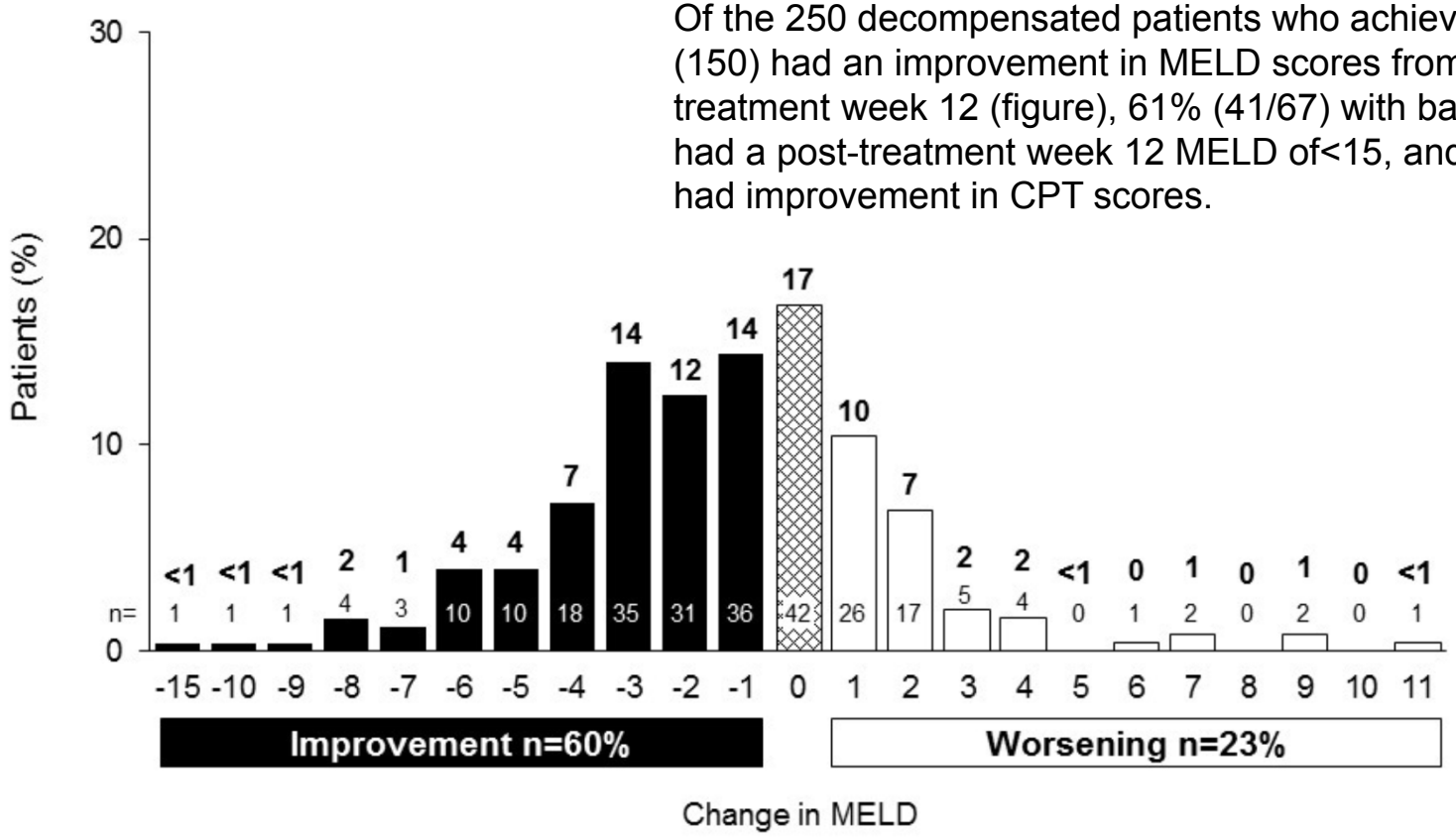
SVR to IFN-free therapies might ameliorate portal hypertension across all BL HVPG strata. However, changes in HVPG seemed to be more heterogeneous among patients with BL HVPG of ≥16 mmHg and a HVPG decrease was less likely in patients with more advanced liver dysfunction.

Mandorfer M, et al. JHepatol 2016;65:692–699.

Encouraging short-term benefits among decompensated patients achieving SVR

Solar 1,2.
N=667

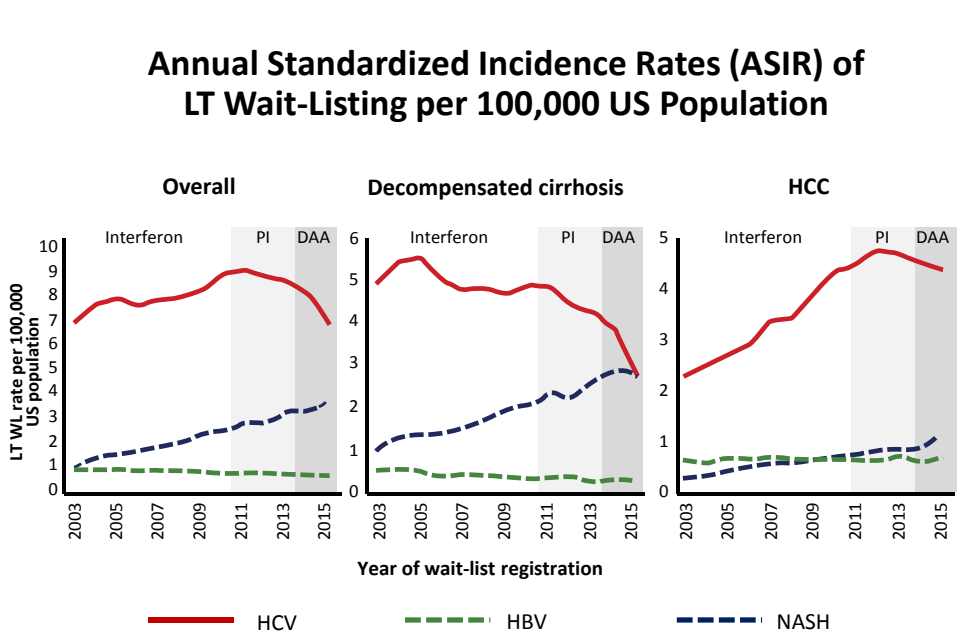
Of the 250 decompensated patients who achieved SVR12, 60% (150) had an improvement in MELD scores from baseline to post-treatment week 12 (figure), 61% (41/67) with baselineMELD≥15, had a post-treatment week 12 MELD of<15, and 66% (164/248) had improvement in CPT scores.

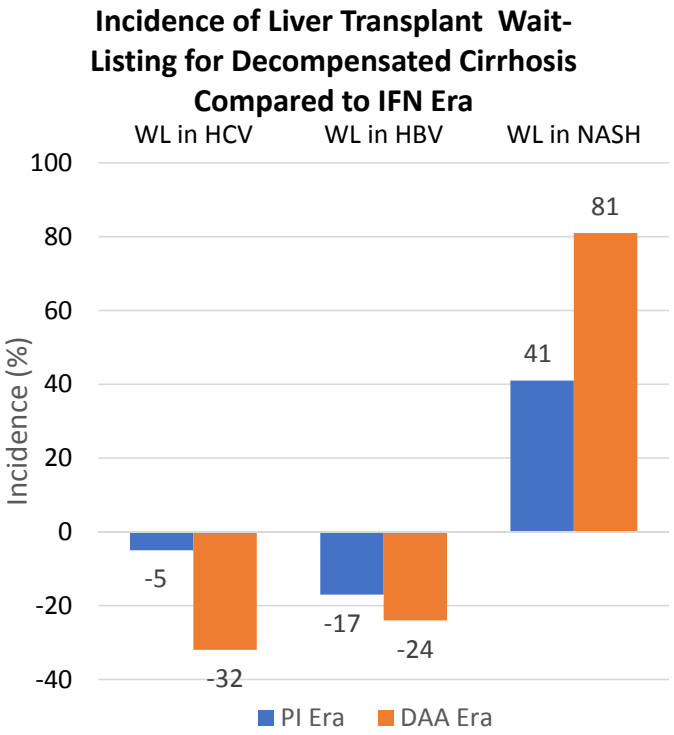


Gane E, et al. AASLD 2015; #1049.

Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015





ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ «Ο ΕΥΑΓΓΕΛΙΣΜΟΣ»

The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH

Flemming JA, AASLD 2016, Poster LB-23

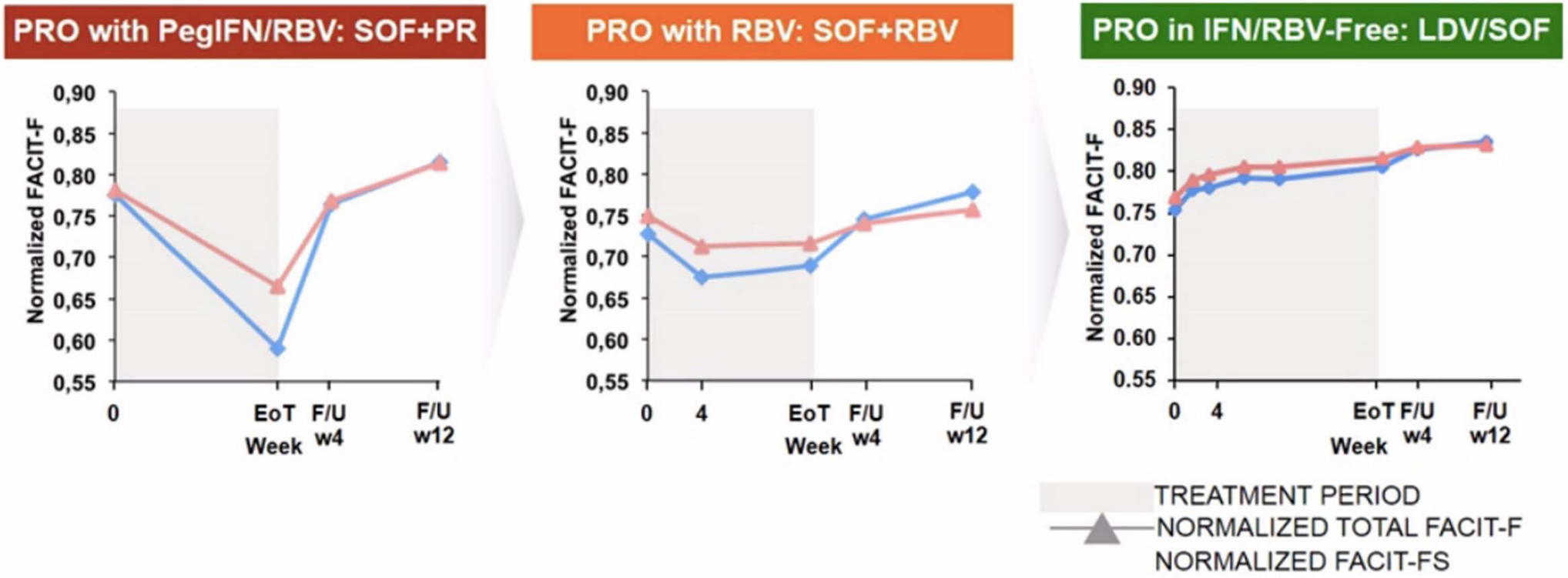
Proportion of patient reaching delisting criteria in real life cohorts

studies	n. pts	Meld baseline	HCC rate	SVR12	Reaching delisting criteria*	delisted
ITACOPS (Italy) 1	216	13 (6-24)	47%	NA	40%	NA
Coilly (France)	151	10±5 (6-32)	56%	88%	26%	6%
Deterding (Germany)	88	NA	0%	74%	38%	NA

* MELD < 15 in studies from Italy and France; Transition from Child B-C to A in Germany

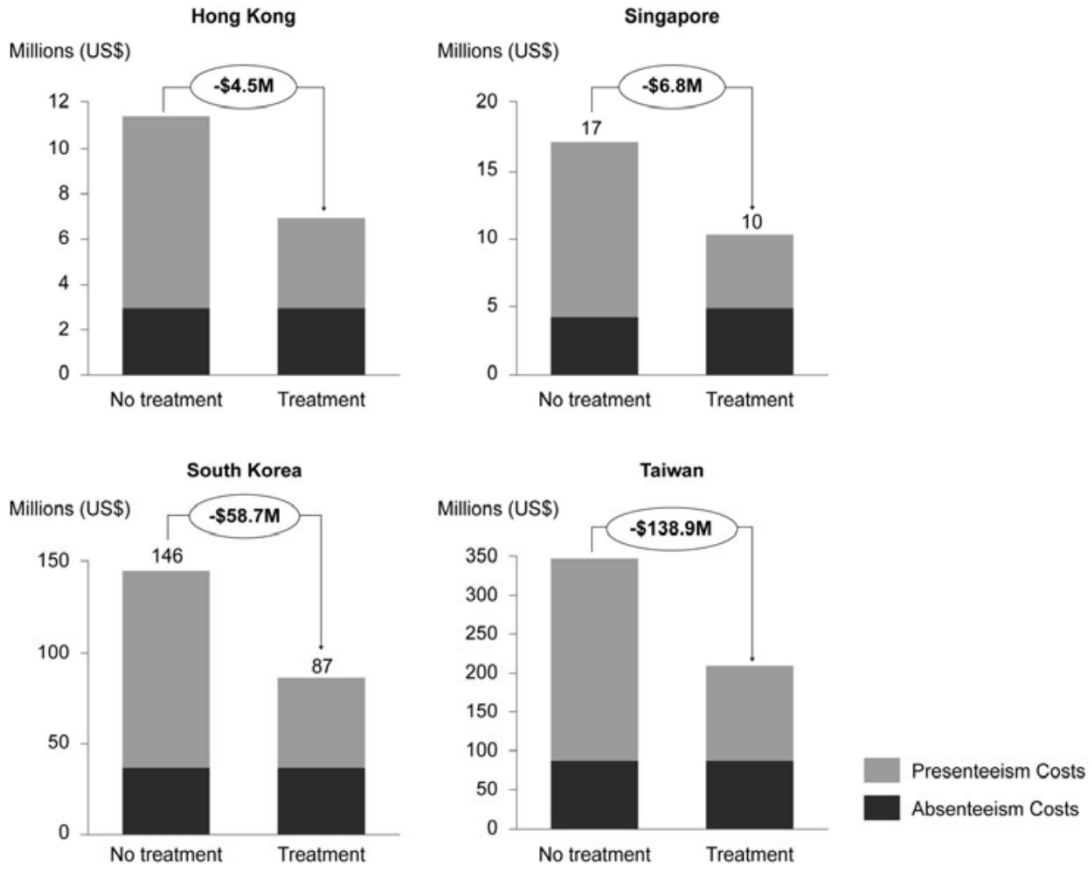
Martini S, et al. AASLD 2015; LB-26, Coilly A, et al. AASLD 2015, #91, Deterding K, et al. Aliment Pharmacol Ther. 2015;42(7):889-901.

Quality of Life
“Patient-Reported Outcomes (PROs)”



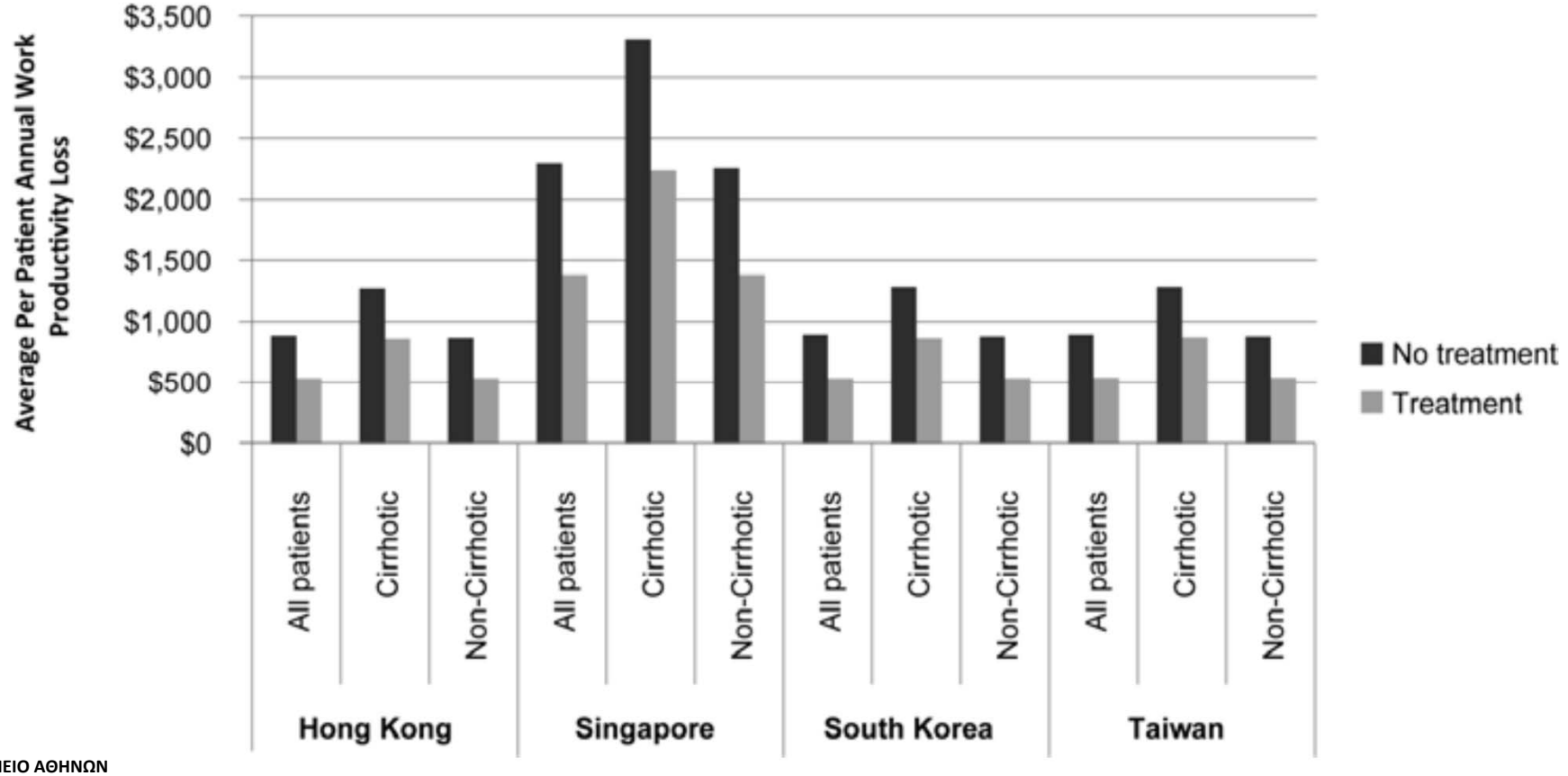
Younossi Z, et al, AASLD 2014;#1445.

Avoided productivity losses resulting from achievement of SVR



Younossi ZM, et al. J Viral Hepat. 2017; [Epub ahead of print].

Reduction in work productivity losses per employed patient



Younossi ZM, et al. J Viral Hepat. 2017; [Epub ahead of print].

Συμπερασματικά..

- Τα DAAs είναι ιδιαίτερα αποτελεσματικά και ασφαλή για την θεραπεία ασθενών με χρονία ηπατίτιδα C.
- Δεδομένα από την καθημερινή κλινική πραγματικότητα αντανακλούν την αποτελεσματικότητα που καταγράφεται στις κλινικές μελέτες.
- Είναι διαθέσιμες πολλές επιλογές με ισχυρά δεδομένα που θα μπορούσαν να συνεισφέρουν στην εξατομίκευση και την προσαρμογή της θεραπείας.
- Η μείωση της διάρκειας θεραπείας είναι δικαιολογημένη σε συγκεκριμένους υποπληθυσμούς ασθενών.
- Η RBV μπορεί να συνεισφέρει στην βελτιστοποίηση των ποσοστών SVR σε δύσκολους ασθενείς.
- Στην επιλογή ενός θεραπευτικού σχήματος θα πρέπει να λαμβάνουμε υπόψη μας το κόστος.

Ερωτήσεις – συζήτηση