Medium and long-term outcomes in HCV infection after DAA treatment

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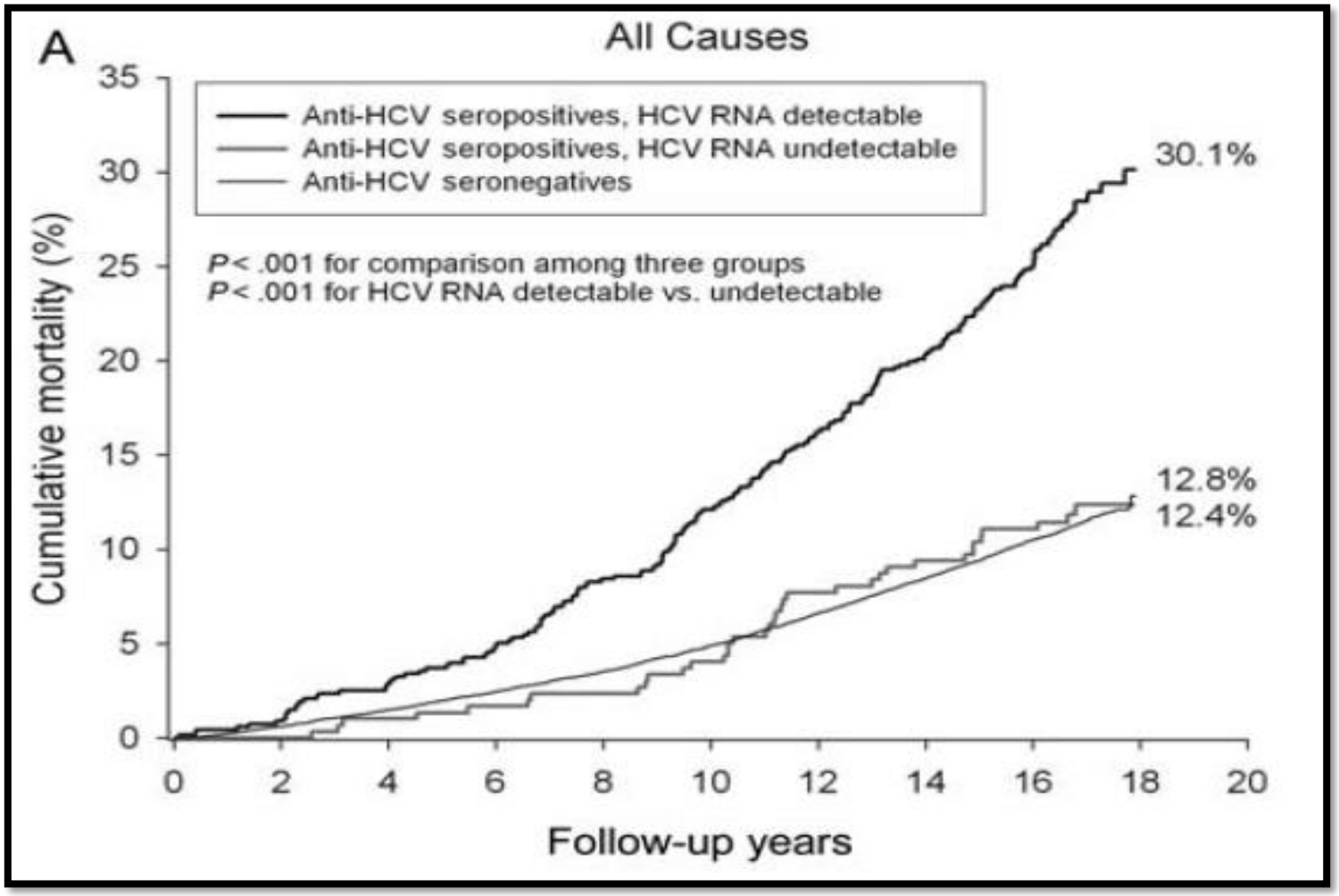
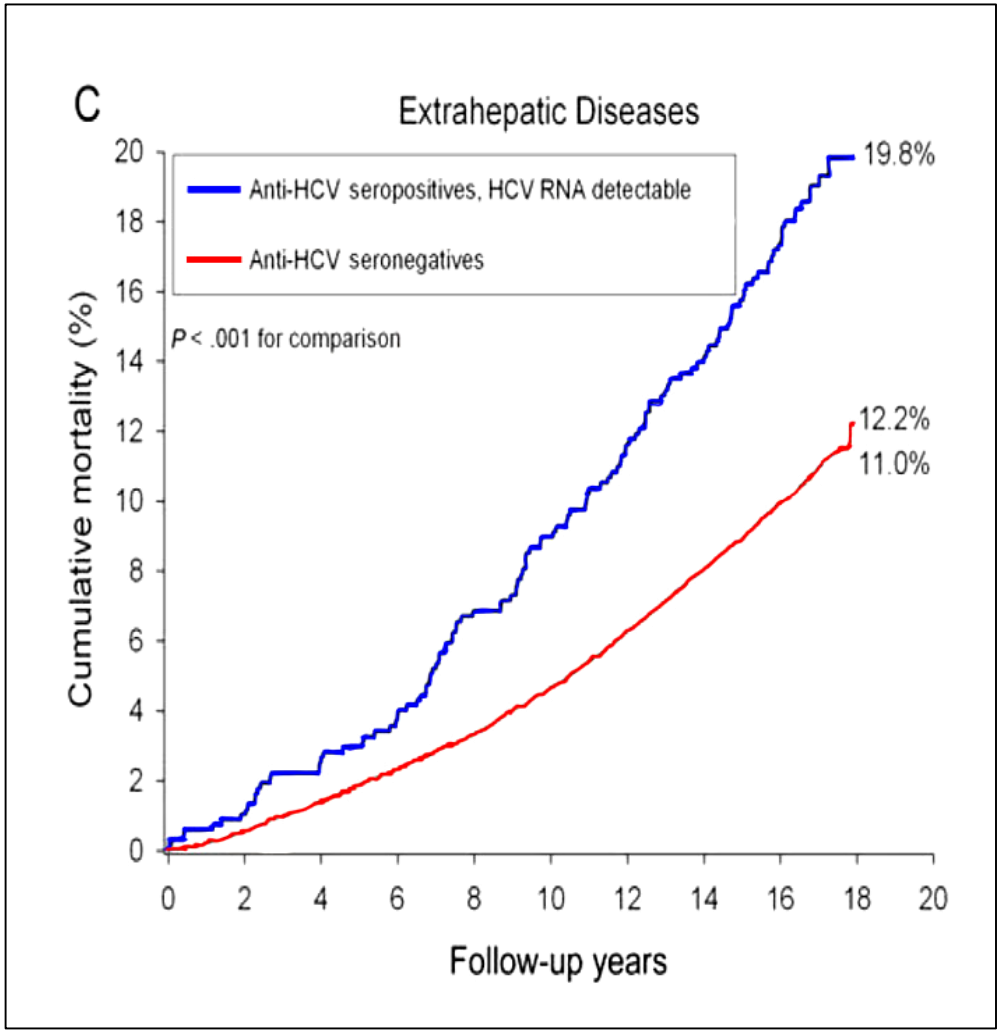
The risk of dying among HCV-infected persons



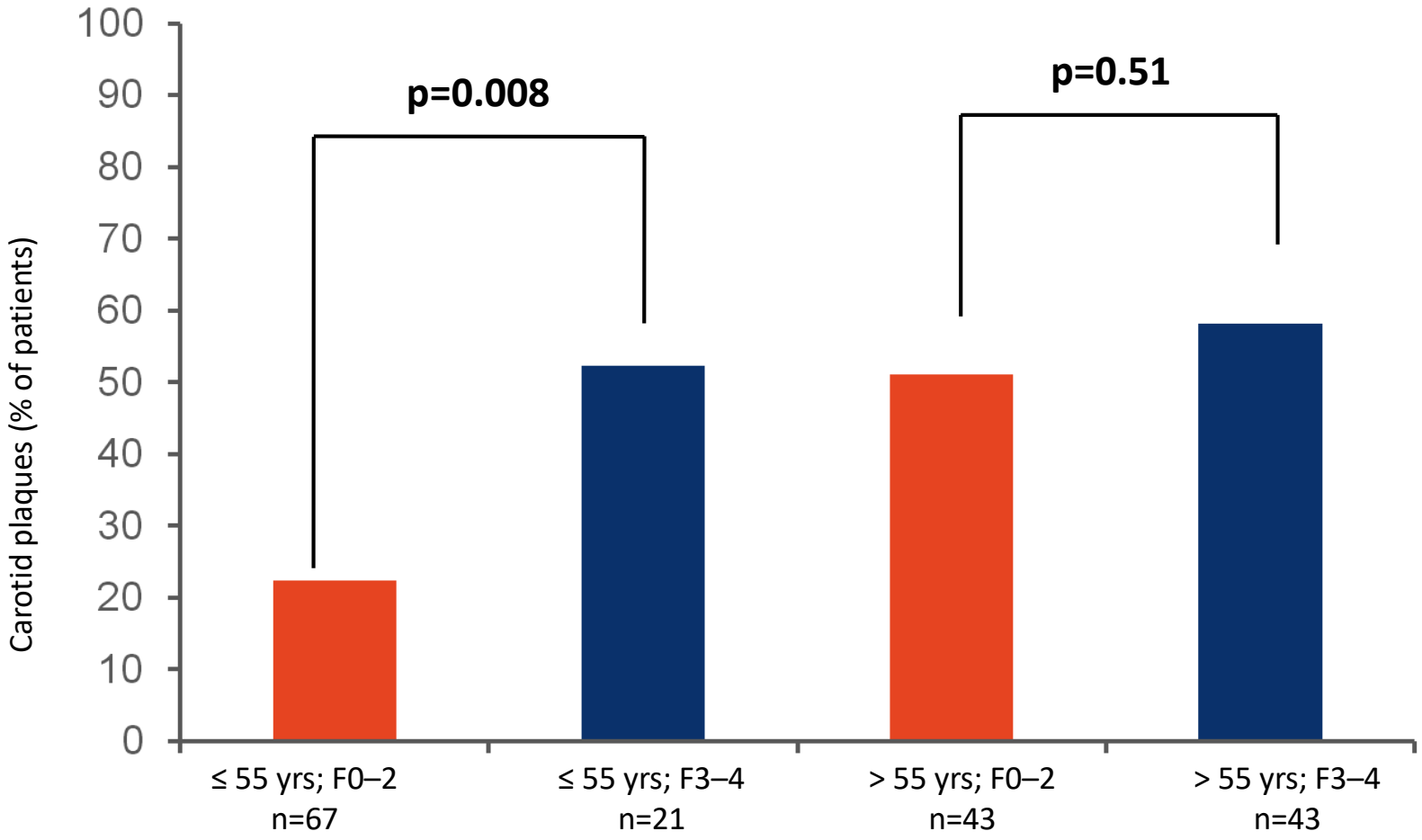
LEE et al, J Infect Dis 2012

The risk of dying of non-liver related causes among HCV-infected persons



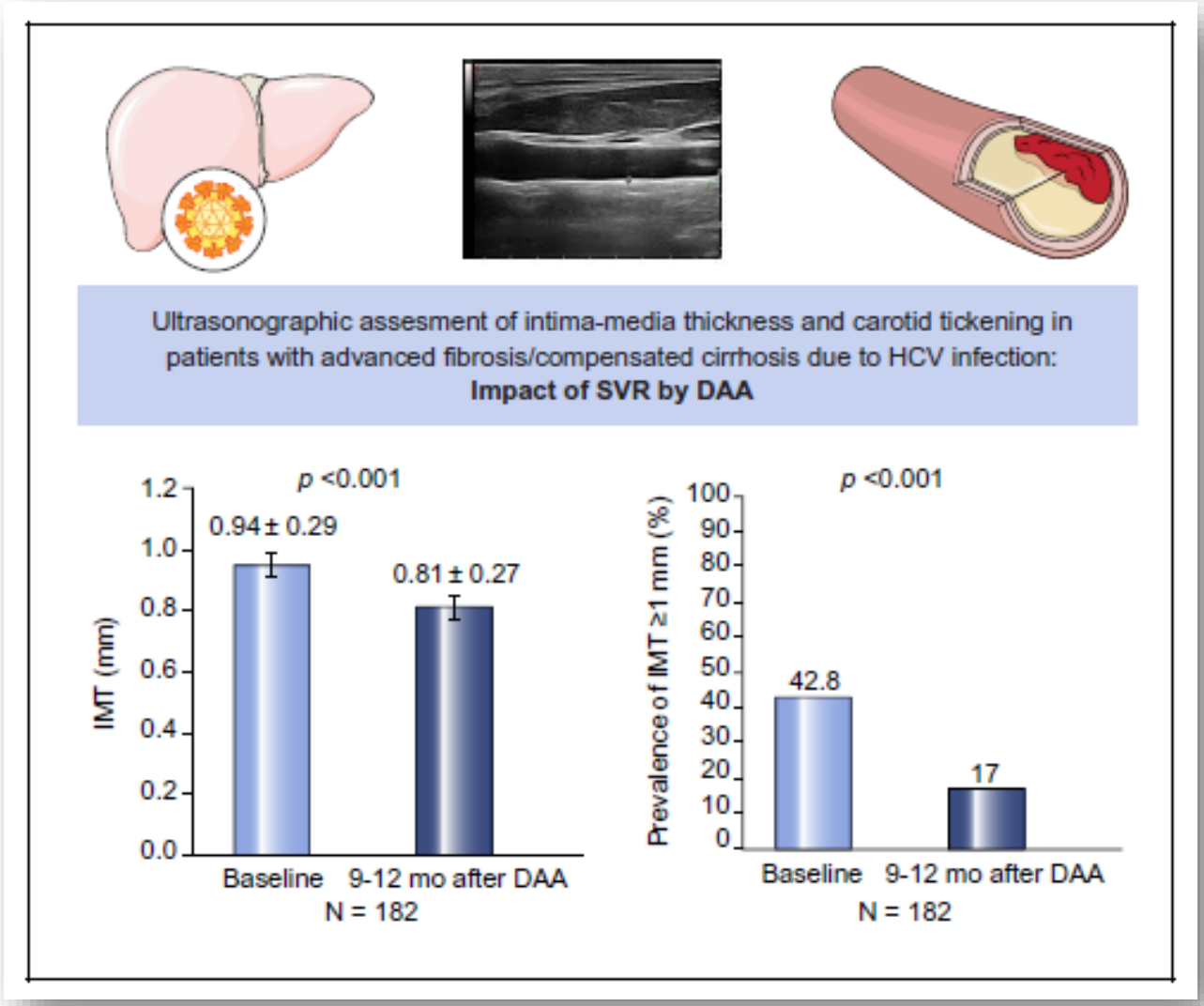
LEE et al, J Infect Dis 2012

Carotid atherosclerosis and HCV



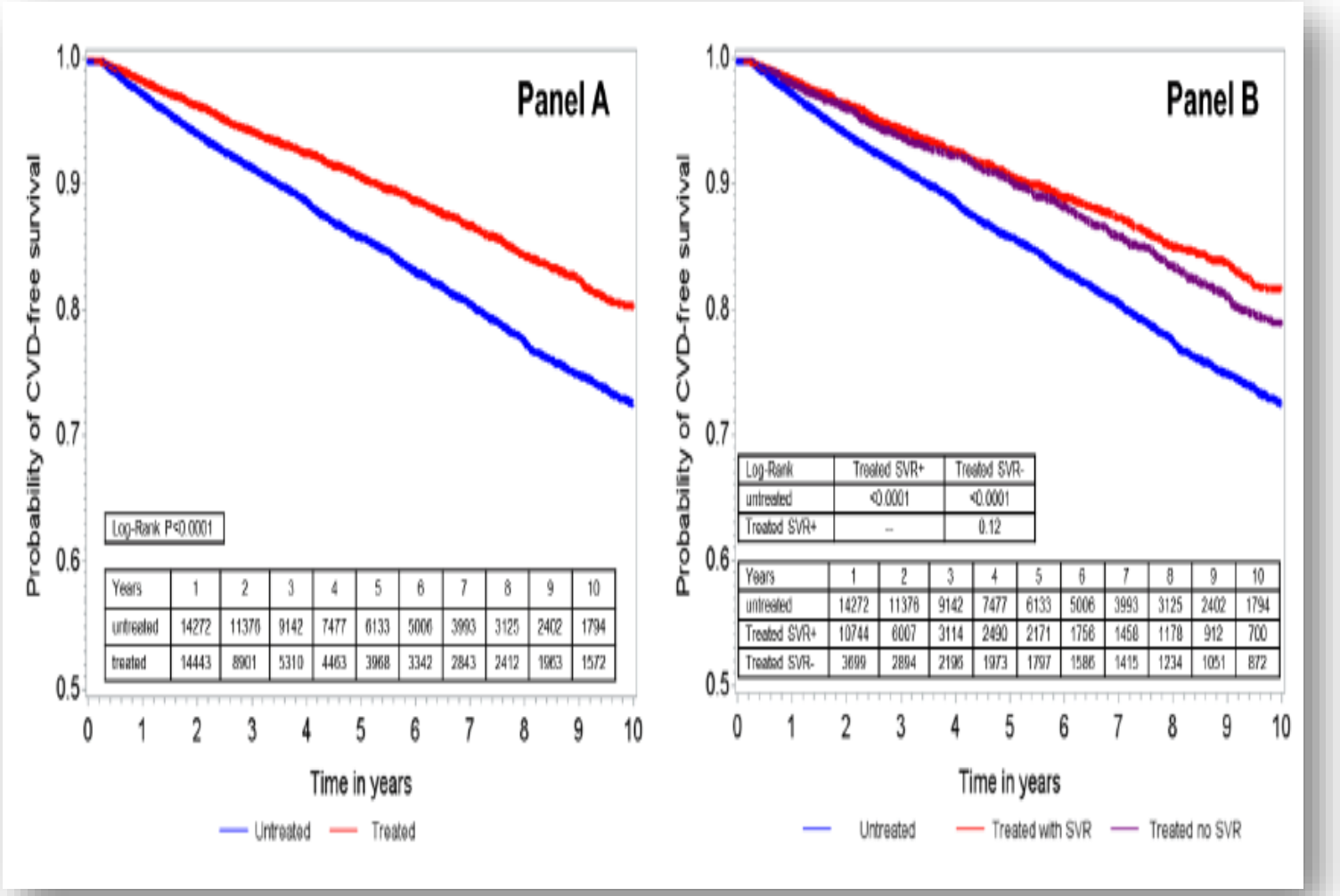
PETTA *et al,* Hepatology 2012

Carotid atherosclerosis after DAA



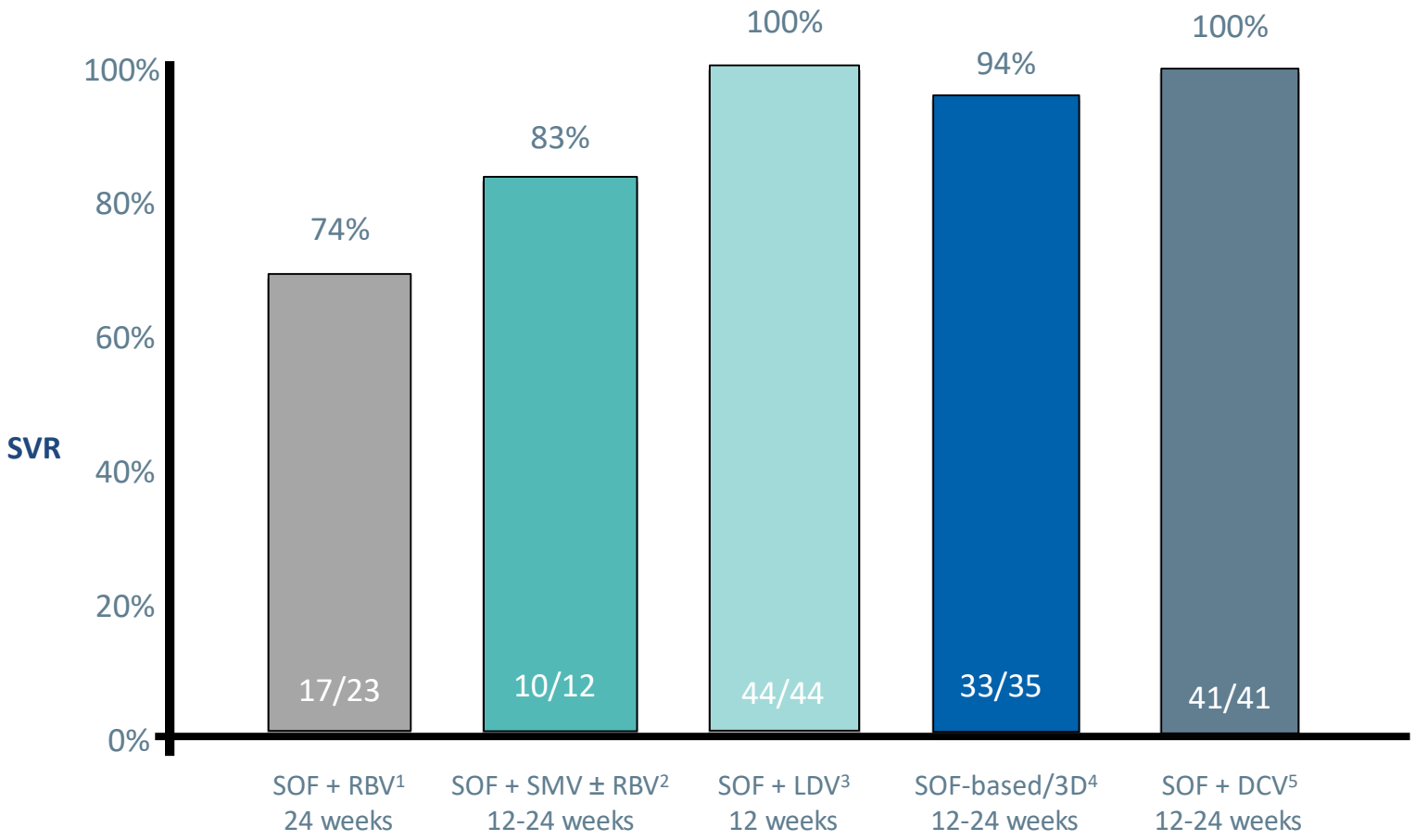
PETTA S et al, J HEP 2018

Outcome after SVR: CARDIOVASCULAR FREE SURVIVAL



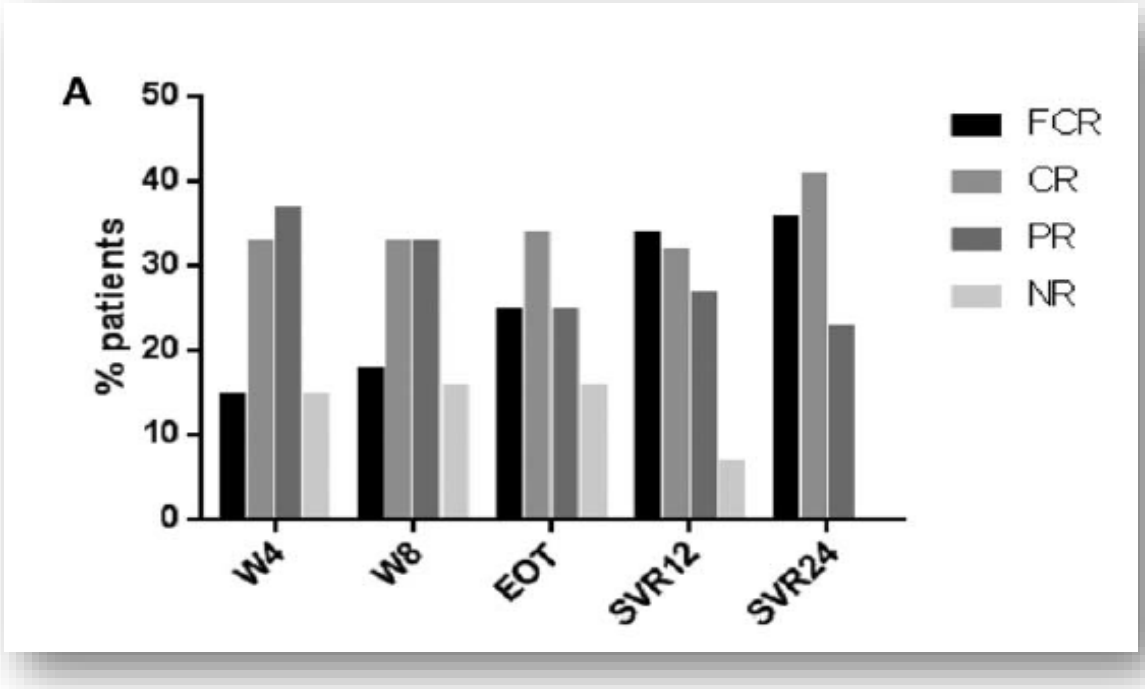
BUTT AA et al, AASLD 2018

SVR after DAA in HCV crioglobulinemia



SAADOUN *et al,* Ann Rheum Dis 2015; SISE *et al,* Hepatology 2016; GRAGNANI *et al,* Hepatology 2016;BONACCI *et al,* Clin Gastro Hepatol 2016; SAADOUN *et al,* Gastroenterology 2017

Clinical response after SVR with DAA in HCV crioglobulinemia



FCR: full complete response; CR: complete response; PR: partial response; NR: non-response

GRAGNANI *et al,* Hepatology 2016

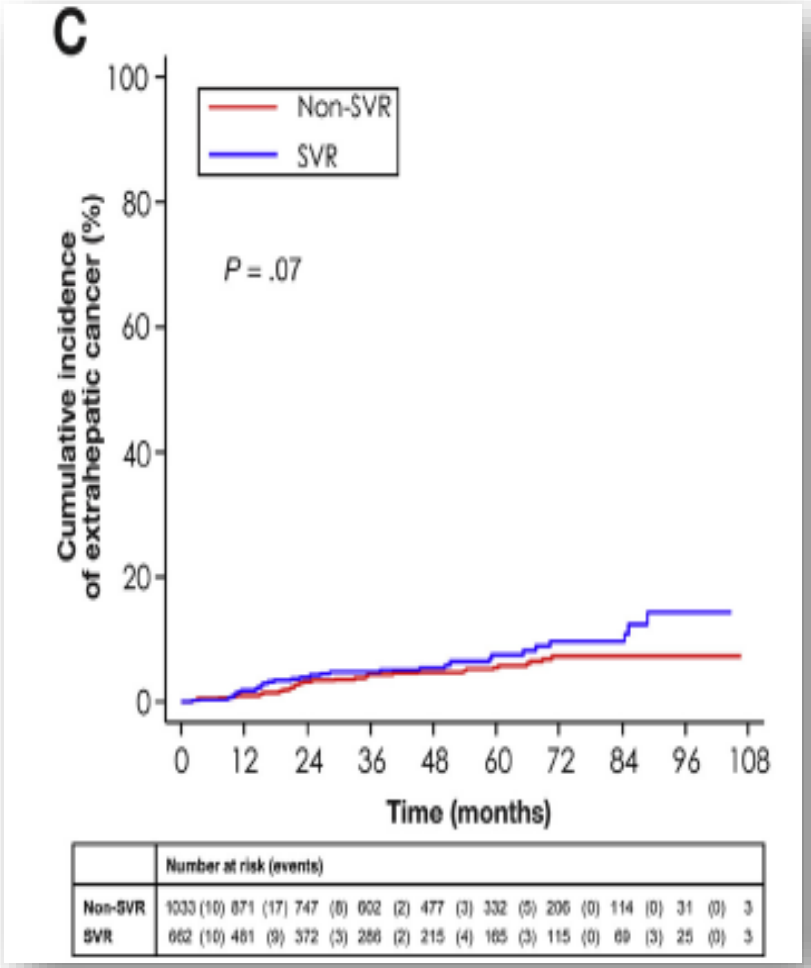
Glycemic control after DAA in DMT2

TABLE 4 Anthropometric, biochemical, and metabolic variations in sustained responders and relapsing/untreated patients

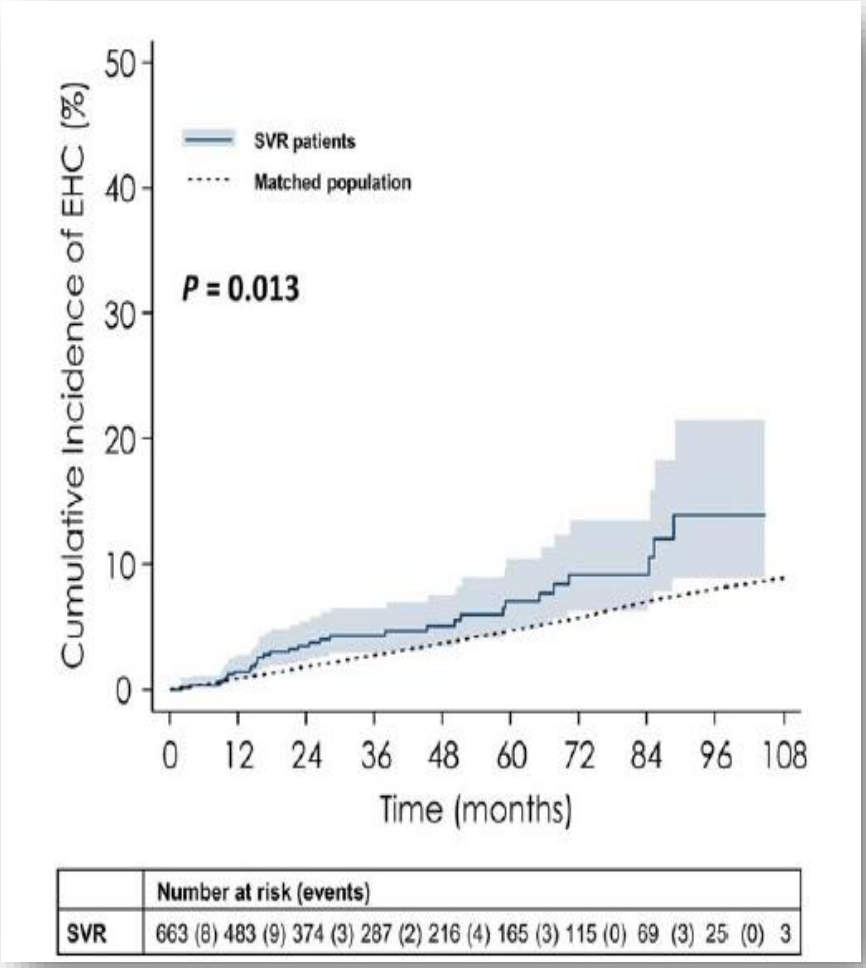
	Group 1 (101 patients)			Group 2 (21 patients)		
	Baseline	End of study	*P*	Baseline	End of study	*P*
AST (IU/mL)[a]	42.3 ± 37.6	28.2 ± 11.0	0.02	40.3 ± 38.4	42.2 ± 39.8	0.85
ALT (IU/mL)[a]	81.2 ± 77.2	36.0 ± 12.0	<0.001	78.7 ± 67.3	82.2 ± 71.6	0.74
GGT (IU/mL)[a]	87.8 ± 81.0	62.5 ± 73.2	0.02	65.2 ± 64.0	67.0 ± 68.1	0.43
Bilirubin (mg/dL)[b]	1.0 (0.6-1.8)	0.8 (0.7-1.1)	0.12	0.9 (0.6-1.3)	1.0 (0.7-1.4)	0.52
Albumin (g/L)[b]	42 (31-48)	44 (33-49)	0.09	43 (34-47)	42 (33-48)	0.78
INR[b]	1.3 (1.0-1.8)	1.0 (1.0-1.5)	0.08	1.2 (1.0-1.7)	1.3 (1.0-2.1)	0.33
Leukocytes ($x10^3$/μL cells)[b]	4.2 (2.2-7.8)	5.4 (3.3-8.2)	0.07	4.4(2.8-6.2)	4.1 (2.3-7.3)	0.64
Platelets ($x10^3$/μL cells)[b]	155 (62-287)	173 (52-274)	0.08	164 (73-245)	162 (68-274)	0.35
Glucose (mg/dL)[a]	152.4 ± 56.4	134.3 ± 41.3	0.002	145.3 ± 30.2	140.0 ± 47.9	0.71
HbA1c (mmoL/moL)[a]	52.2 ± 15.4	46.5 ± 16.2	<0.001	53.4 ± 9.5	55.3 ± 20.6	0.78
HOMA-IR[a]	5.2 ± 2.5	3.1 ± 1.6	<0.001	4.9 ± 2.6	4.6 ± 2.3	0.29
Body weight (kg)[a]	75.3 ± 13.7	77.9 ± 19.8	0.02	76.6 ± 19.3	76.9 ± 20.7	0.56

CIANCIO A et al, J Med Virol 2018

Risk of non-hepatic cancers after SVR

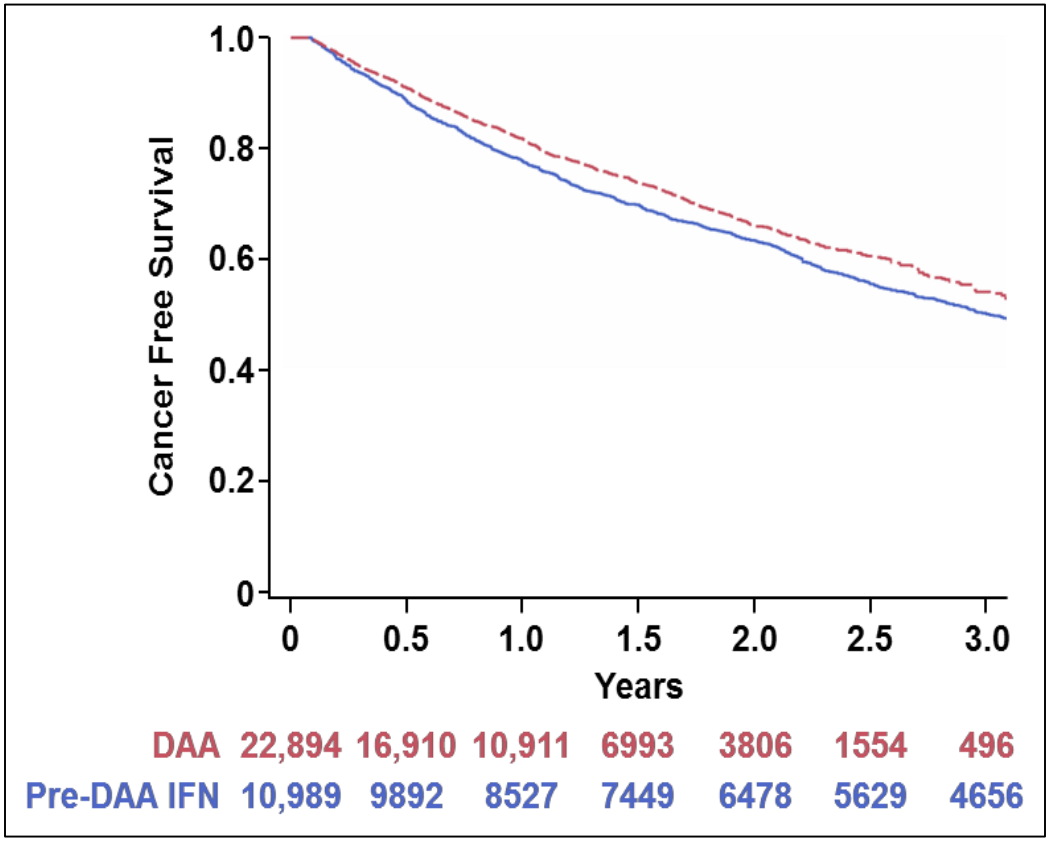


NAHON P et al, Gastroenterology 2017



ALLAIRE M et al, Hepatology 2018

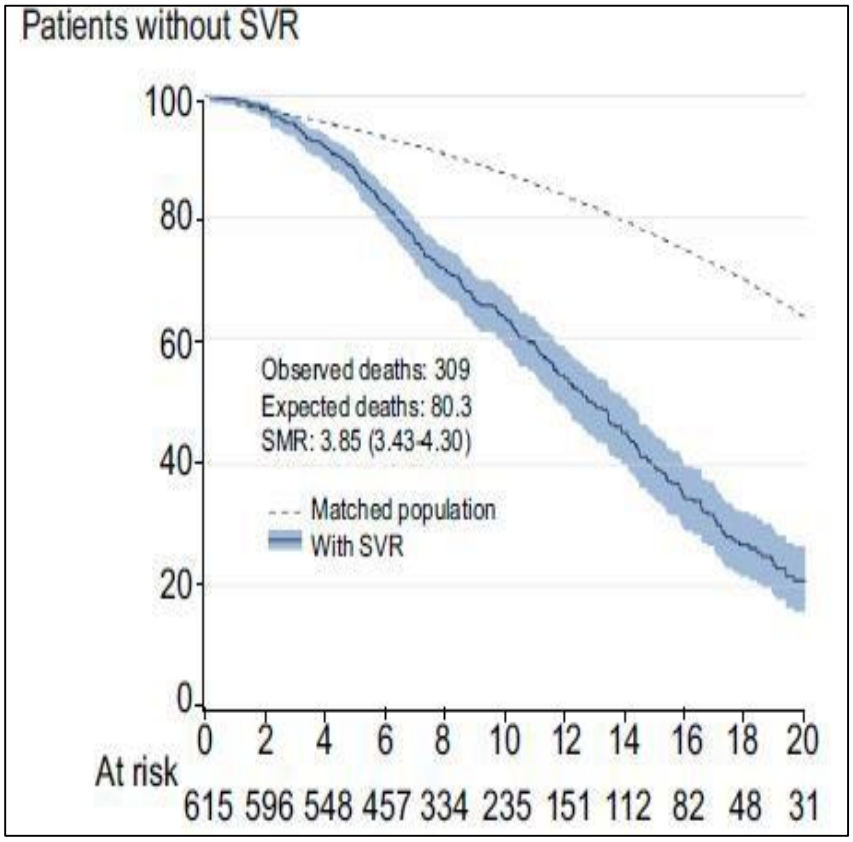
Risk of non-hepatic cancers after DAA compared to IFN

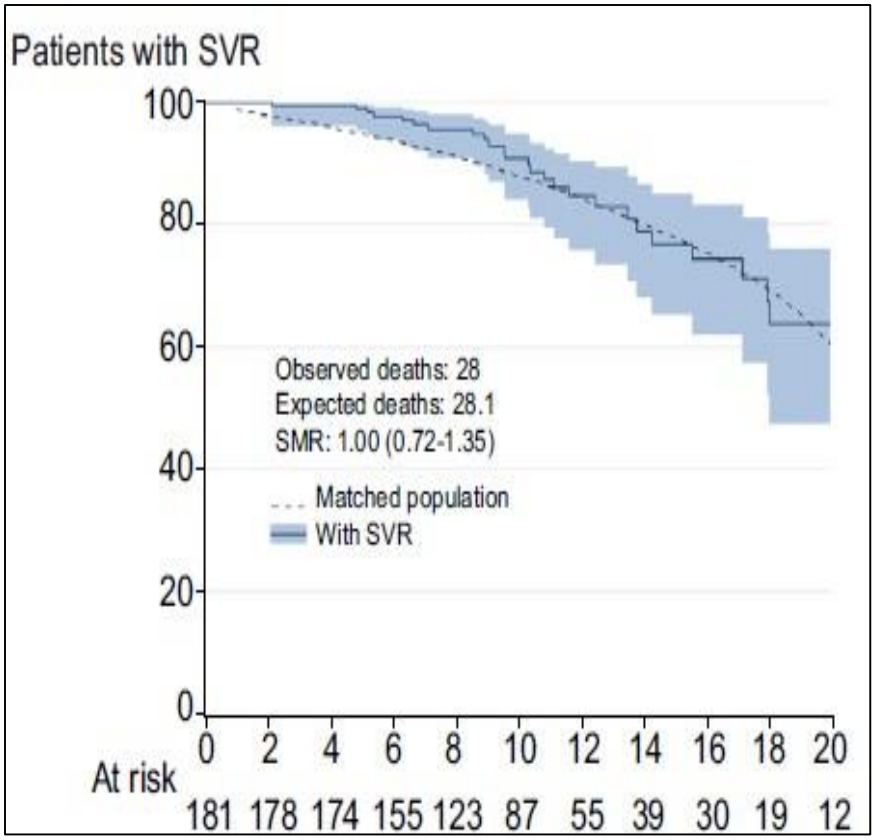


DAA treatment associated with reduced risk of total non-hepatic cancer (significant for prostate and lung, NS for NHL and bile duct)

CHOKKALLINGAM et al, EASL 2018

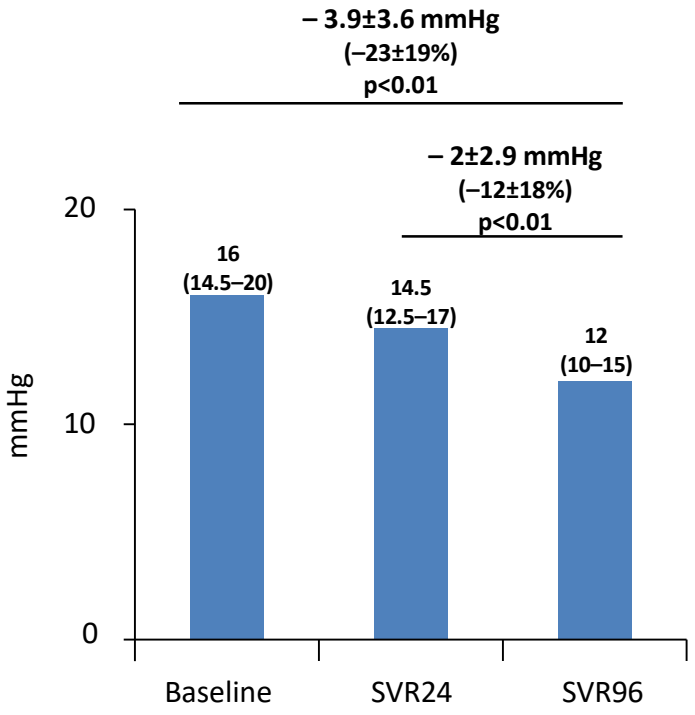
Outcome after SVR:
SURVIVAL AFTER P/R TREATMENT

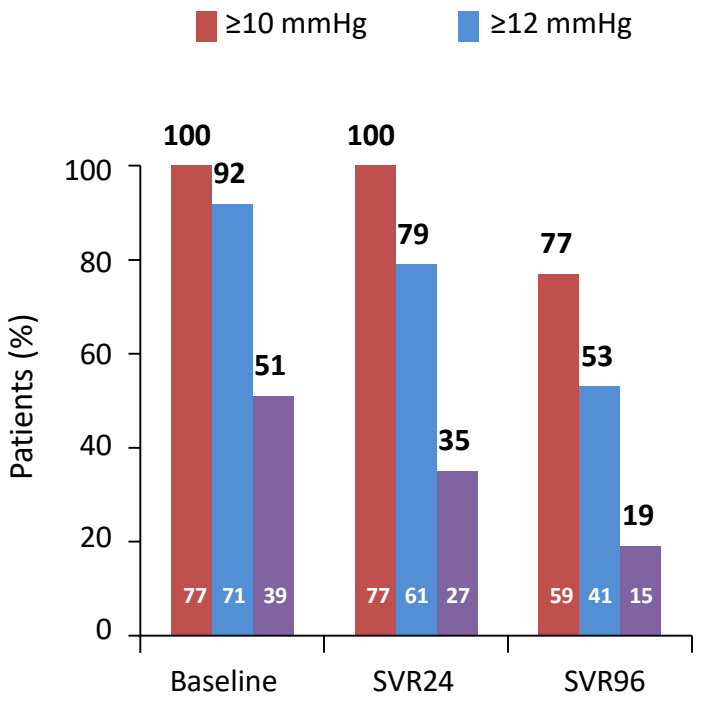




BRUNO S, et al J Hepatol 2017

Outcome after SVR with DAA: PORTAL HYPERTENSION



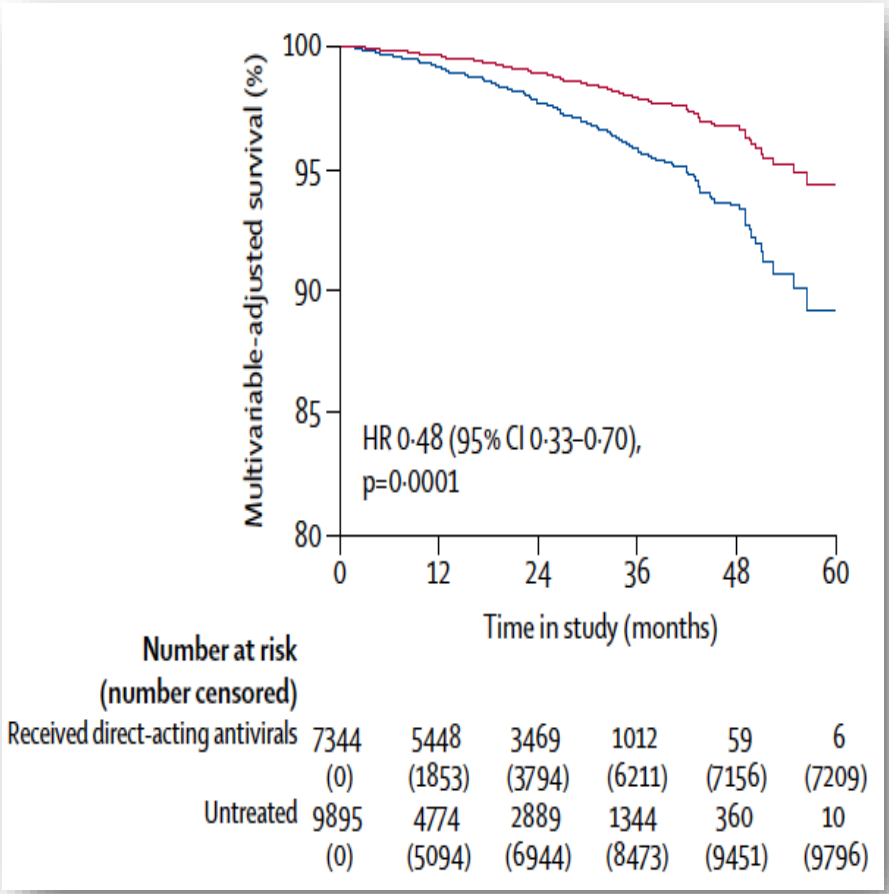


LENS S, et al. Gastroenterology 2017; LENS S, et al. ILC 2018

Outcome after DAA: ALL CAUSE MORTALITY

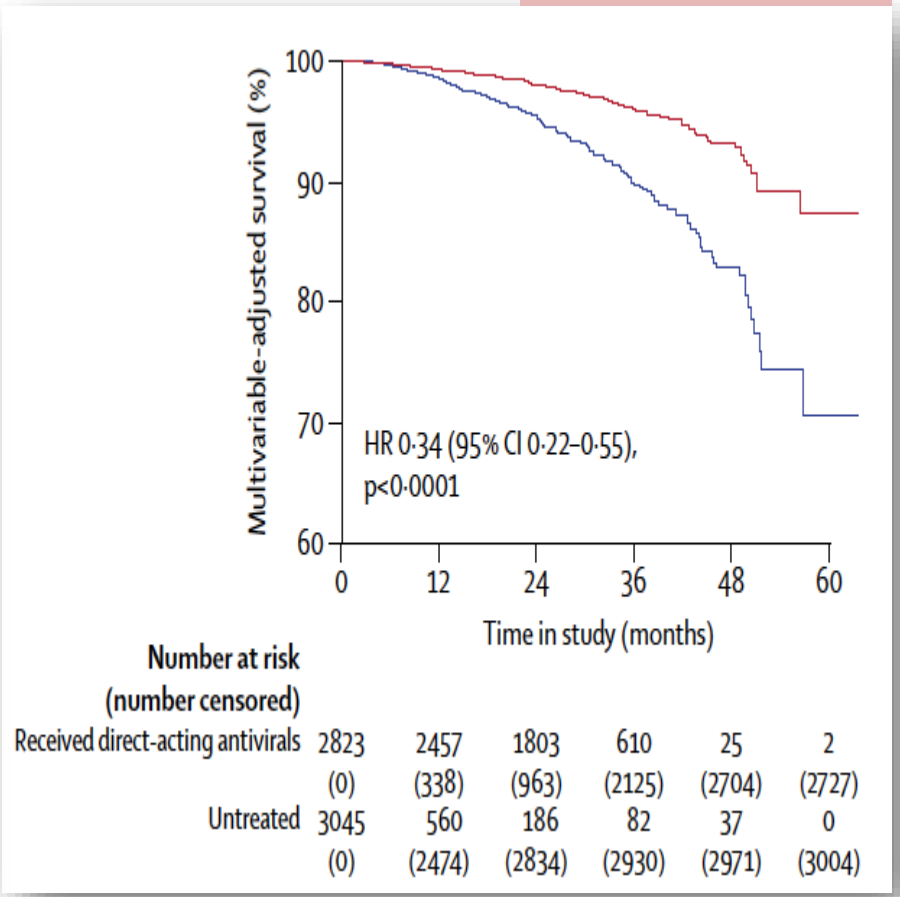
Treated — Untreated

Global survival



Number at risk (number censored)						
Received direct-acting antivirals	7344	5448	3469	1012	59	6
	(0)	(1853)	(3794)	(6211)	(7156)	(7209)
Untreated	9895	4774	2889	1344	360	10
	(0)	(5094)	(6944)	(8473)	(9451)	(9796)

Cirrhosis survival



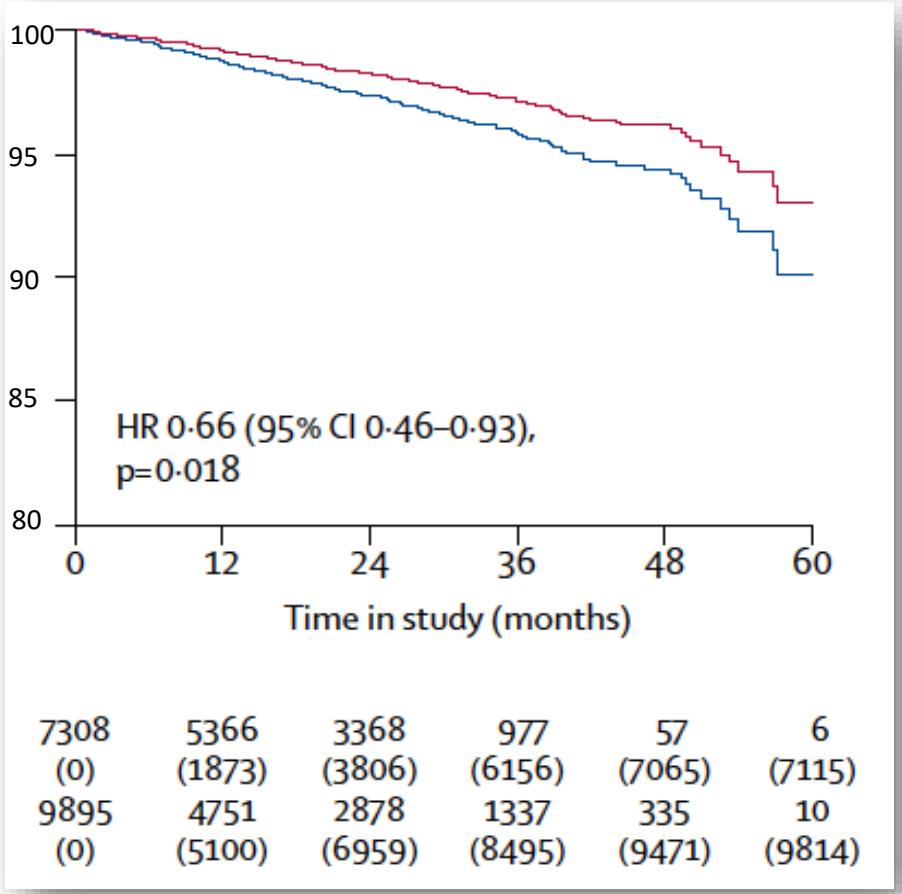
Number at risk (number censored)						
Received direct-acting antivirals	2823	2457	1803	610	25	2
	(0)	(338)	(963)	(2125)	(2704)	(2727)
Untreated	3045	560	186	82	37	0
	(0)	(2474)	(2834)	(2930)	(2971)	(3004)

CARRAT F, et al. Lancet 2019

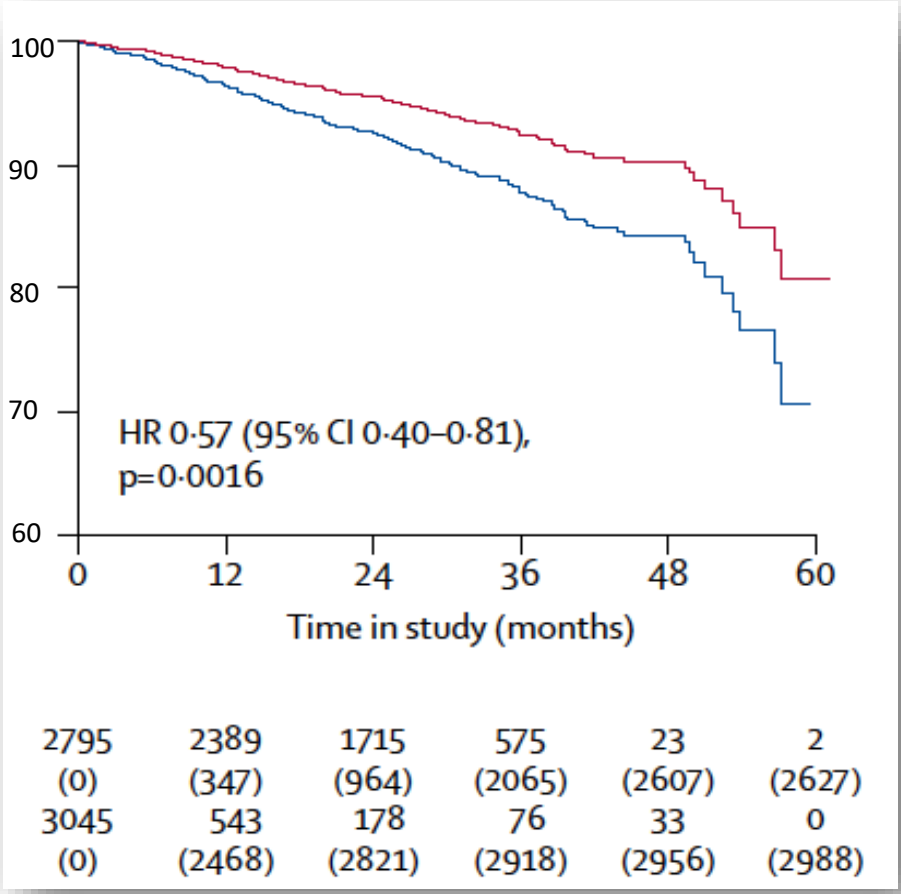
Outcome after DAA: HEPATOCELLULAR CARCINOMA

Treated — Untreated

Global incidence

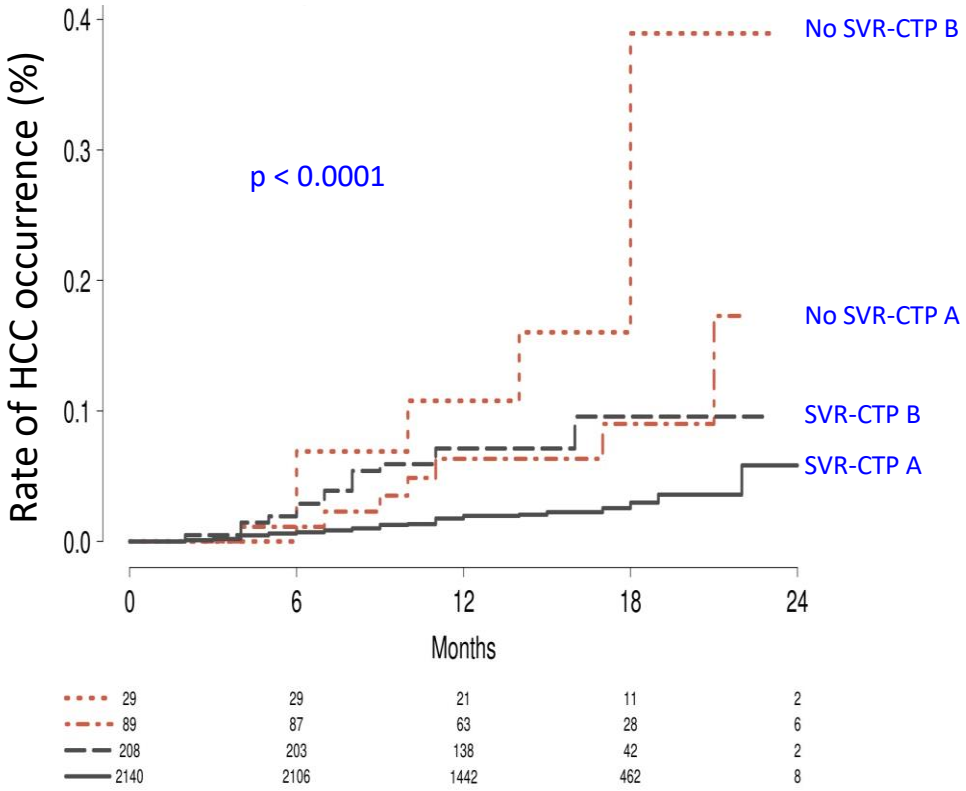


Cirrhosis incidence

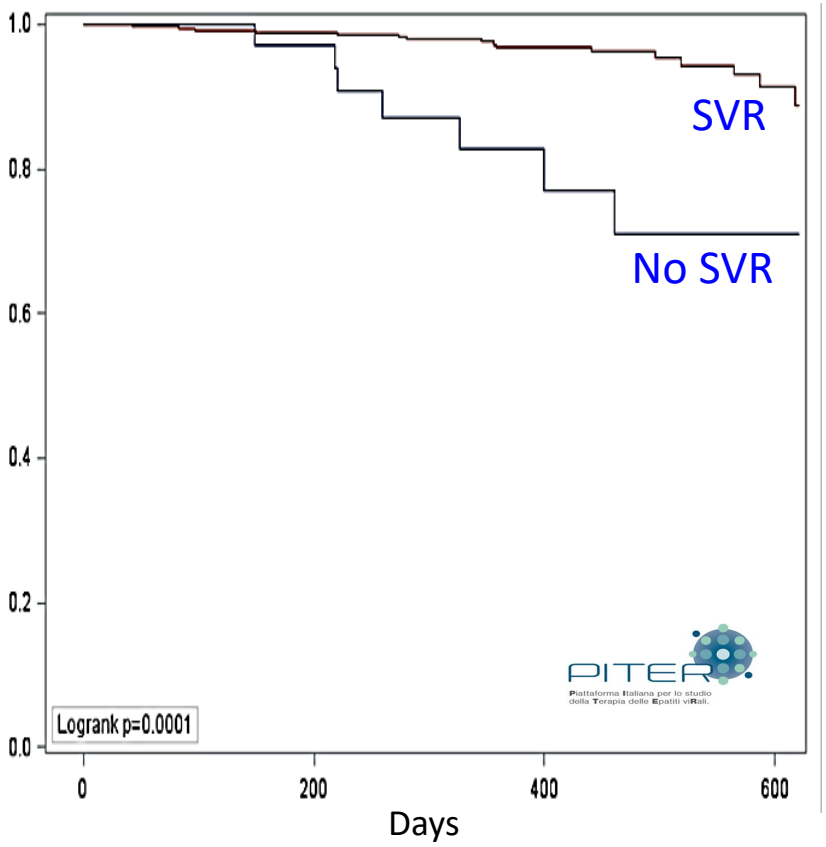


CARRAT F, et al. Lancet 2019

Outcome after DAA: HEPATOCELLULAR CARCINOMA

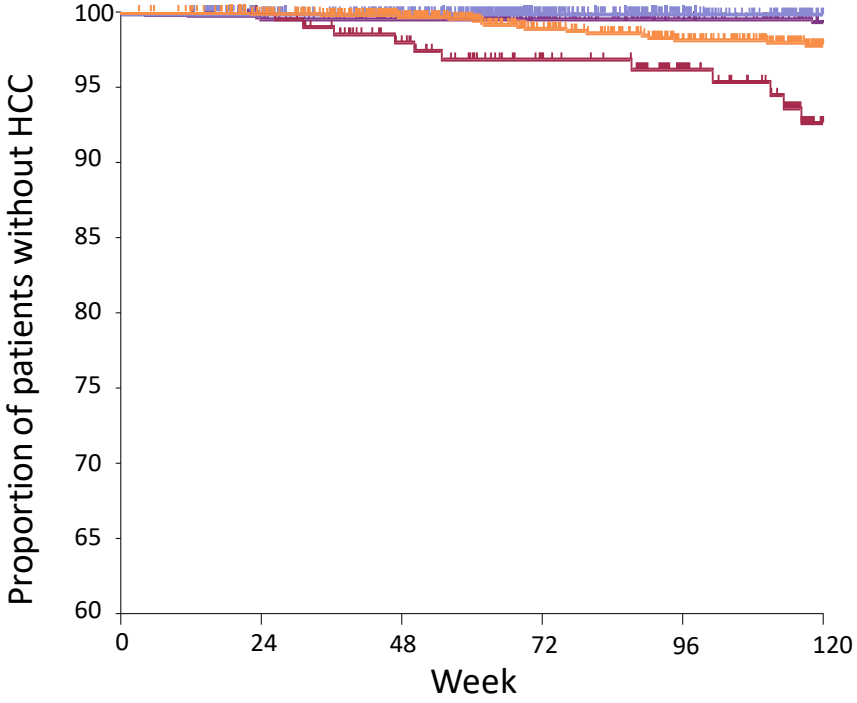


CALVARUSO V et al, Gastroenterology 2018



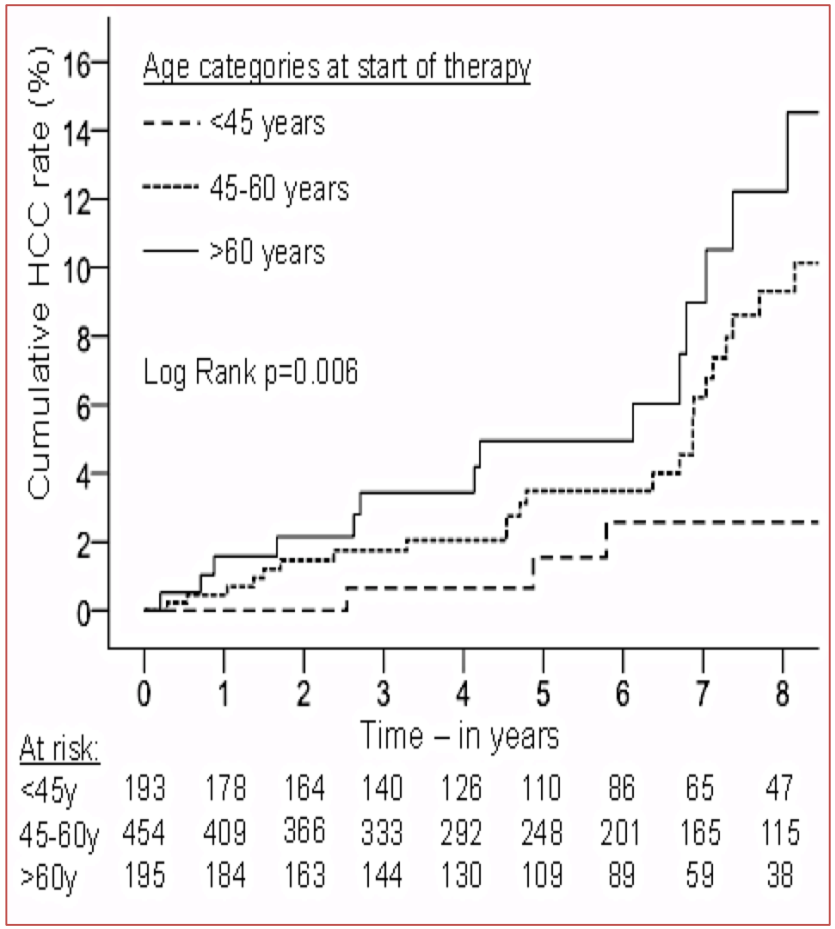
PITER cohort; data elaborated by Stefano Rosato

Outcome after DAA: HEPATOCELLULAR CARCINOMA



F2	N= 1490	1453	1380	1176	1070	965
F3	N= 858	832	782	648	572	508
CPT A	N= 1037	1014	868	677	592	466
CPT B+C	N= 205	200	185	174	151	90

Integrated Analysis: Gilead Long-Term SVR Registries, EASL 2018



VAN DER MAEER et al, J Hepatol 2017

PITER
Piattaforma Italiana per lo studio della Terapia delle Epatiti viRali.

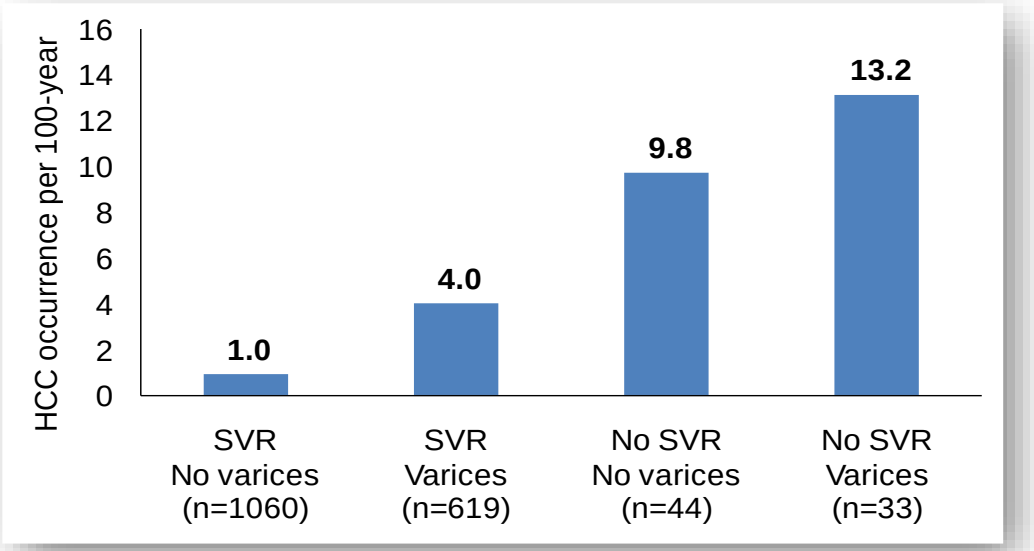
Outcome after DAA: HEPATOCELLULAR CARCINOMA

Variables independently associated to *de-novo* HCC

Variables	Crude OR	CI 95%		Adjusted OR	CI 95%	
Age	1.04	1.02	1.07	1.05	1.02	1.08
Gender M/F	0.8	0.5	1.3	0.72	0.42	1.24
Genotype 3/Others	1.1	0.4	2.1	1.6	0.5	1.9
Diabetes	1.7	1.01	3	1.3	0.6	1.5
Albumin <2.8mg/dl	3.3	1.1	12.5	4.4	1.4	14
Bilirubin>1.5	2.68	1.7	4.4	1.9	1.1	3.39
BMI>25 vs≤25	1.4	0.9	2.3	1.4	0.8	2.4
Liver fat	0.7	0.4	1.3	0.9	0.5	2.4
Platelets ≤100,000	3.0	1.8	4.9	2.3	1.4	4.0

PITER Collaborative Group AASLD 2018; data elaborated by Stefano Rosato

Outcome after DAA: HEPATOCELLULAR CARCINOMA



	Patients	p-years	HCC	Rate
ALL	1766	2057	50	2.4
Platelets >110 and LSM<25 kPa	637	742	5	0.7
Platelets >110 and LSM≥25 kPa	177	202	6	3.0
Platelets ≤110 and LSM<25 kPa	347	411	18	4.4
Platelets ≤110 and LSM≥25 kPa	320	388	9	5.1
SVR				
Platelets >110 and LSM<25 kPa	620	729	4	0.5
No SVR				
Platelets >110 and LSM<25 kPa	17	13.7	1	7.3

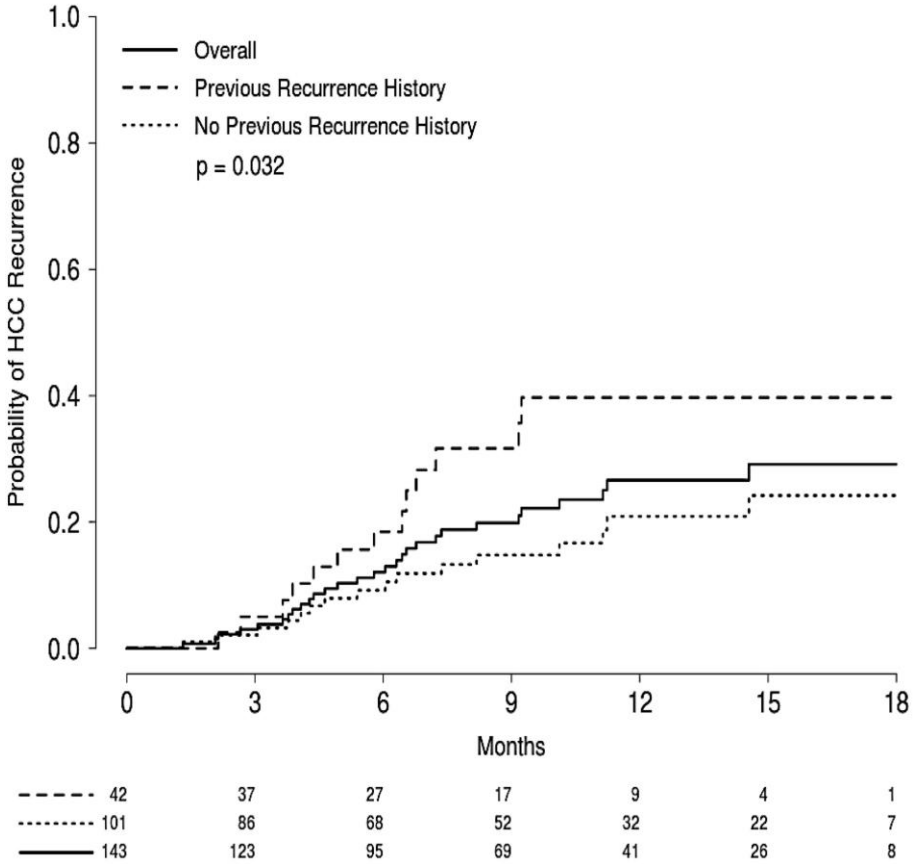
LLEO A et al, DLD in press

Outcome after DAA: HEPATOCELLULAR CARCINOMA recurrence

Author	Recurrence rate	Author	Recurrence rate
Conti 2016	28.8%	Ngata 2017	27.1%
Lei-Zeing 2016	0	Ogawa	17.5%
Pol 2016	13%	Okhi 2017	35.0%
Pol 2016	7.6%	Minami 2017	47.9%
Zavaglia 2016	3.2%	Ikeda 2017	34.6%
Torres 2016	0	Gheoghe 2017	20.0%
Rinaldi 2016	6.7%	Sangiovanni 2017	32.7%
Tokoro 2016	59.1%	Singal 2017	45.9%
Tsuda 2016	25.0%	Granata 2017	27.7%
Reig 2017	27.3%	Urabe 2017	38.5%
Virlogeoux 2017	47.8%	Yasui 2017	14.3%
Cabibbo 2017	20.3%	Bielen 2017	14.6%

(24 studies, 1820 patients)

Outcome after DAA: HEPATOCELLULAR CARCINOMA recurrence



RISK FACTORS FOR RECURRENCE	MULTIVARIABLE MODEL		
	HR	[95% CI]	p-value
Main tumor size > 2.5 cm	2.73	[1.23, 6.06]	0.014
History of Prior Recurrence	2.22	[1.02, 4.83]	0.043

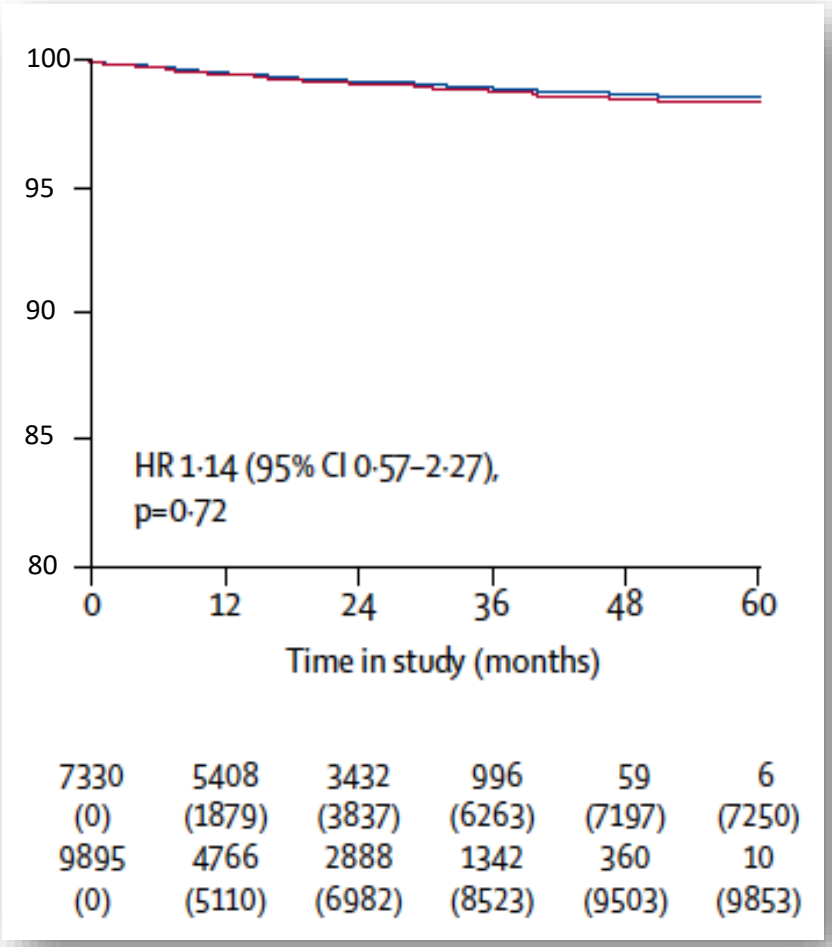
Overall 6- 12- and 18-month HCC recurrence rate: 12%, 26.6% and 29.1% respectively.

CABIBBO G. et al. Aliment Pharmacol Ther. 2017

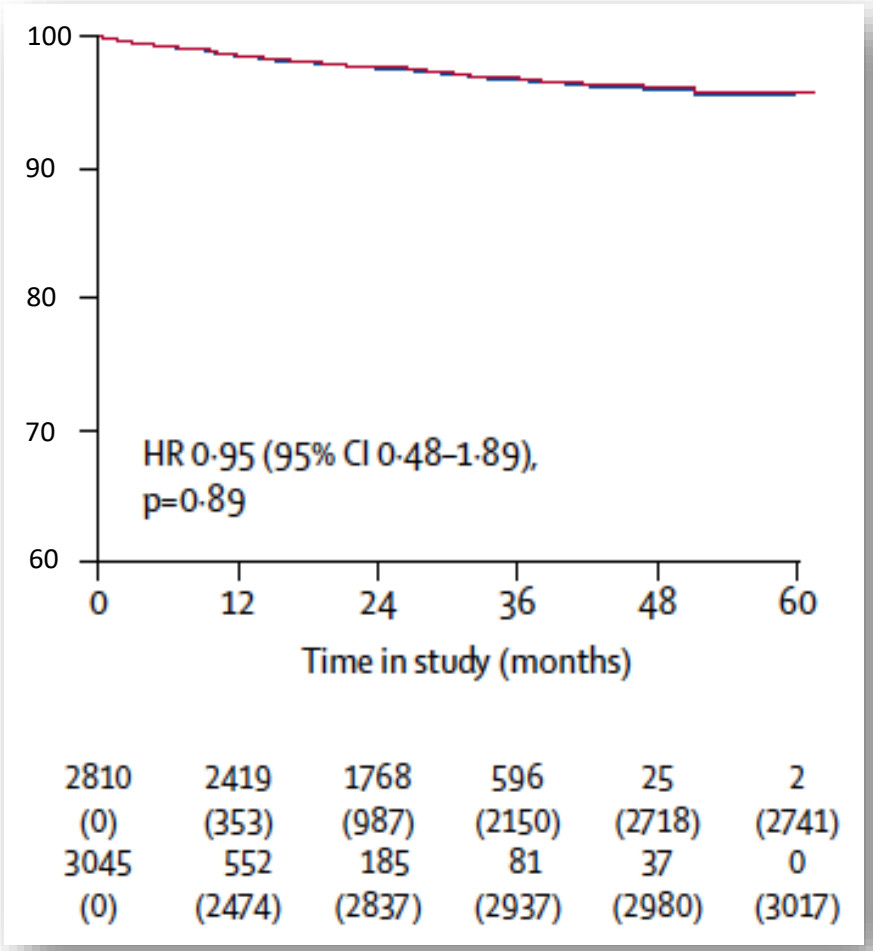
Outcome after DAA: DECOMPENSATION

Treated — Untreated

Global incidence



Cirrhosis incidence



CARRAT F, et al. Lancet 2019

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Outcome after DAA: DECOMPENSATION

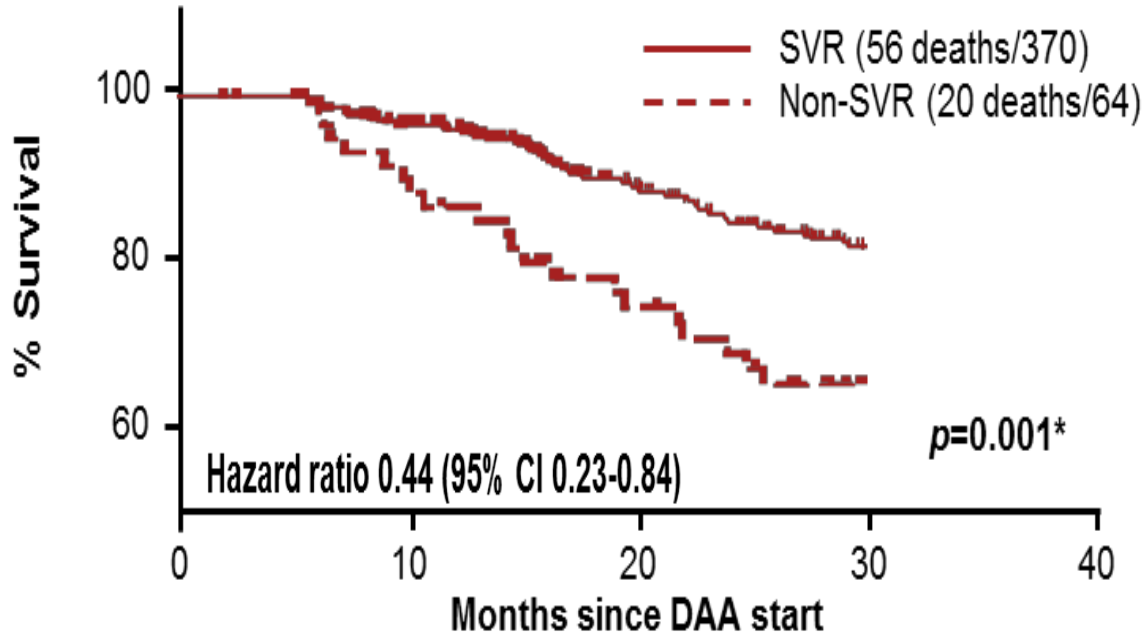
Variables independently associated to deterioration of CHILD-PUGH score

Variables	Crude OR	CI 95%		Adjusted OR	CI 95%	
Age	0.9	0.98	1.0	1	1	1
Gender M/F	0.9	0.64	1.3	1	0.7	1.5
HCC	1.7	0.9	3.0	1.8	1.1	3.3
Genotype 3/Others	1.1	0.6	1.9	1	0.5	1.9
Diabetes	0.9	0.9	1.9	1	0.6	1.5
Albumin <3.5mg/dl	2.4	0.4	3.6	1.4	0.5	5.0
Bilirubin>1.5	1.4	0.9	2.0	1.1	0.7	1.7
BMI>25 vs≤25	1.01	0.69	1.4	0.9	0.7	1.4
Liver fat	0.89	0.6	1.4	1.1	0.7	1.8
Platelets ≤100,000	1.6	1.1	2.3	1.7	1.2	2.4

PITER Collaborative Group AASLD 2018; data elaborated by Stefano Rosato

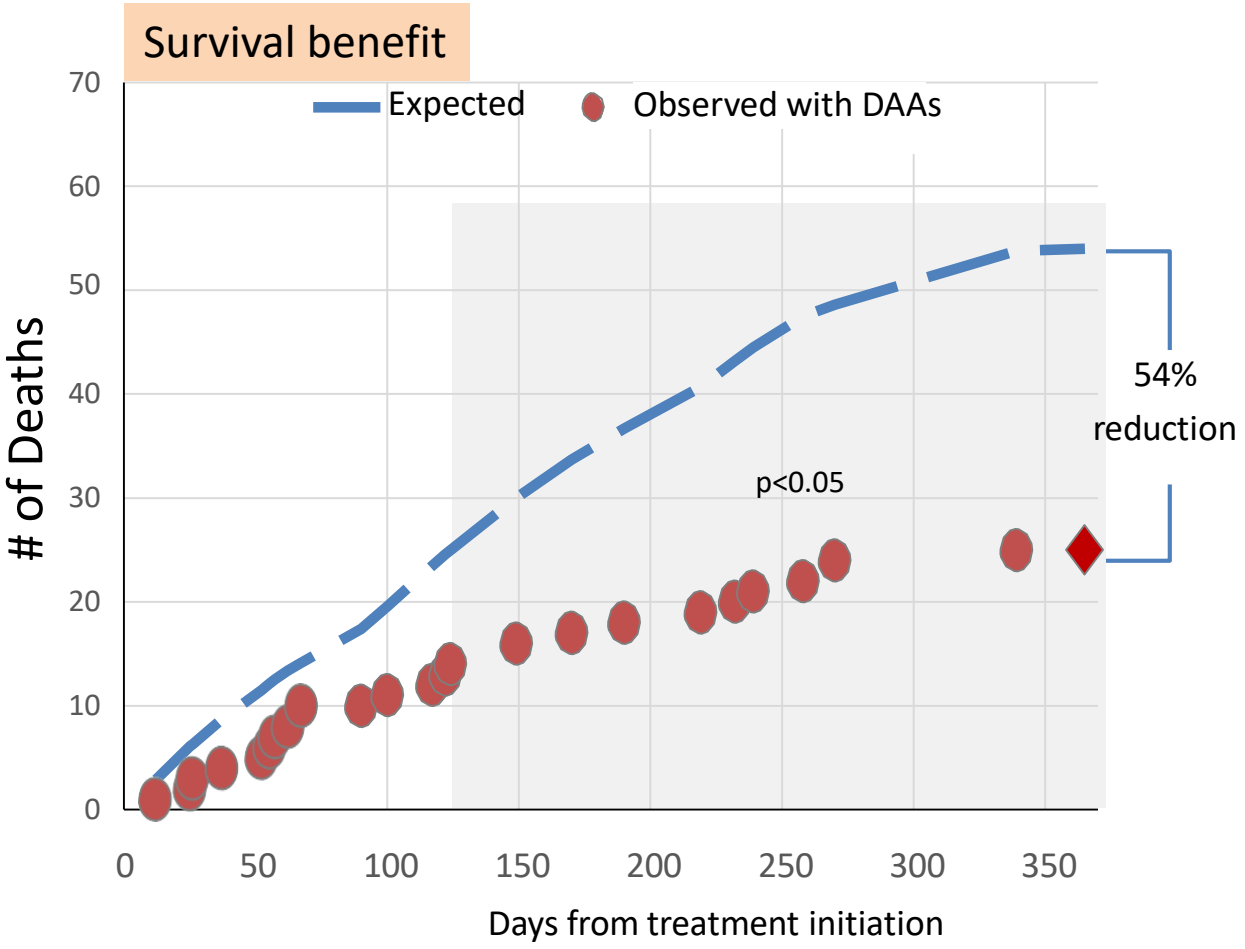
Outcome after DAA: DECOMPENSATED SUBJECTS

Transplant-Free survival



CHEUNG MCM et al, EASL 2018

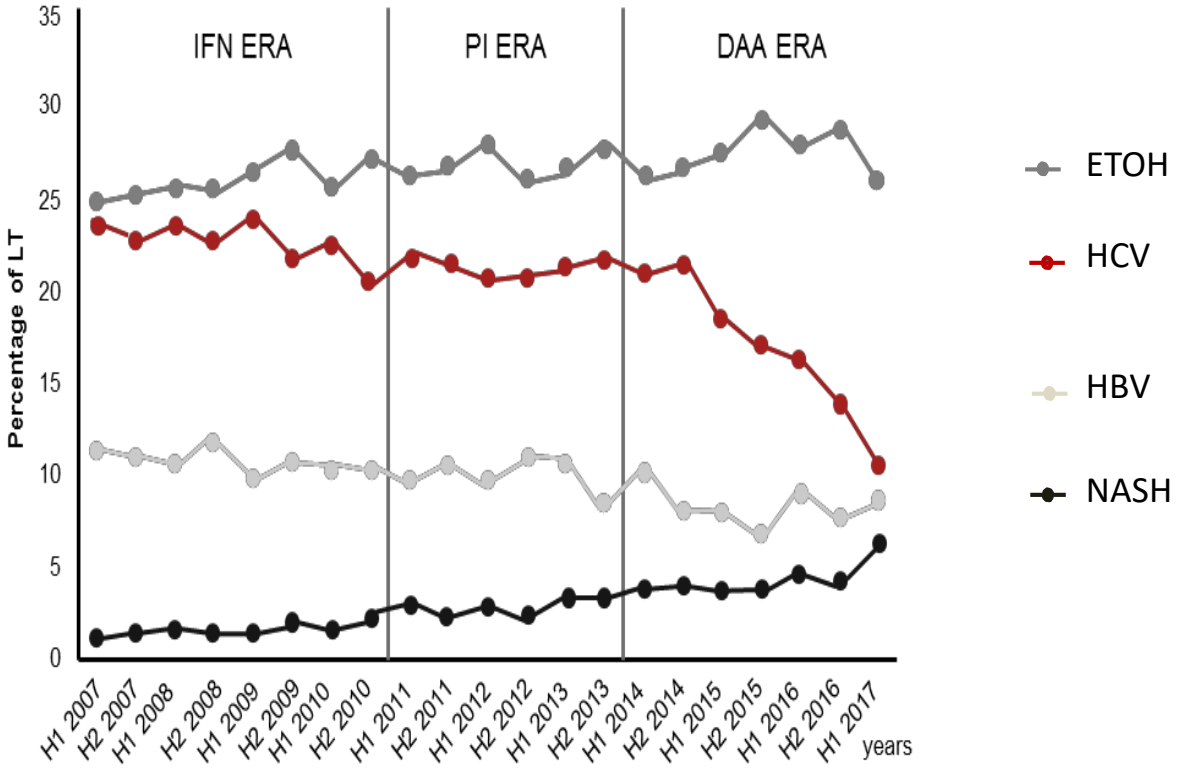
Outcome after DAA: DECOMPENSATED SUBJECTS



KIM et al, EASL 2018

Outcome after DAA: DECOMPENSATED SUBJECTS

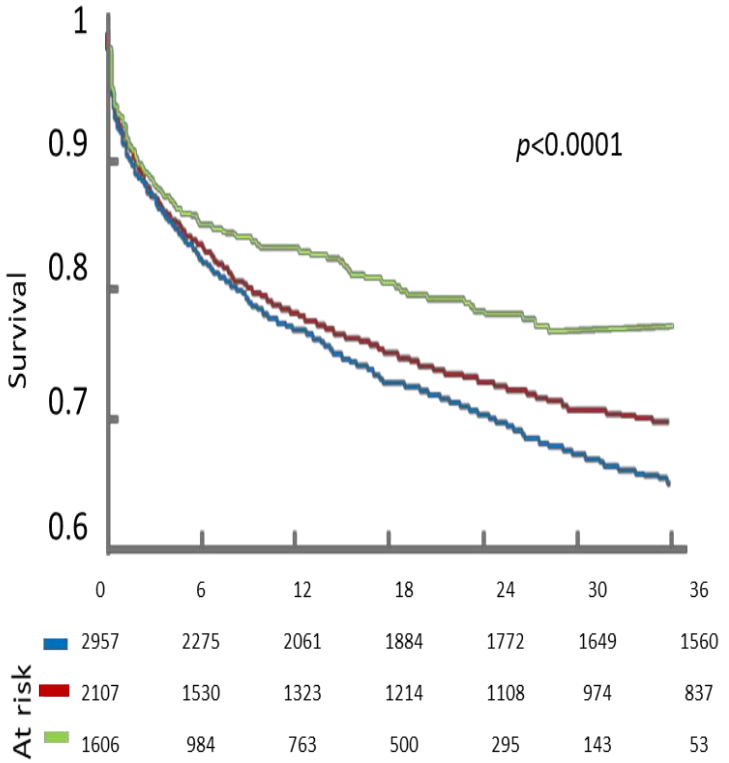
Percentage of Liver Transplants by Indication (ELTR)



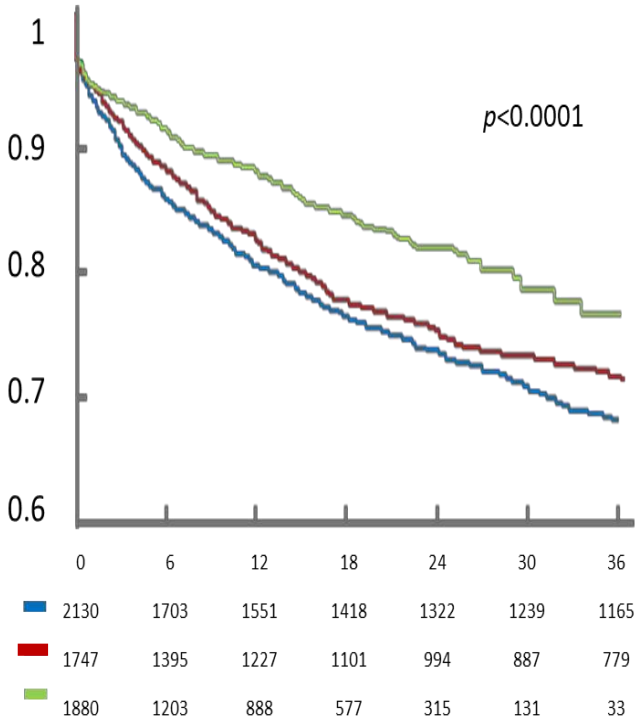
BELLI L et al, J Hepatol 2018

Outcome after DAA: TRANSPLANTED SUBJECTS

Survival post-LT of decompensated cirrhosis



Survival post-LT of HCC



DAA era (2014-2017)
PI era (2011-2013)
IFN era (2007-2010)

BELLI L et al, J Hepatol 2018

Conclusions

After HCV eradication:

- Liver related complications are unusual in **subjects without cirrhosis** and regression of extra-hepatic manifestions are more frequent
- Also in **compensated cirrhosis** a reduction of PH and the risk of CVD can be seen on short and long term FU
- A progressive decrease of **HCC** incidence seems to be an attainable goal but many subjects remain still at risk due to concomitant comorbidities
- The liver function recovery and reduction of global risks in subjects with **decompensated disease** seems to be less evident but of great impact on transplantation lists

Thanks to

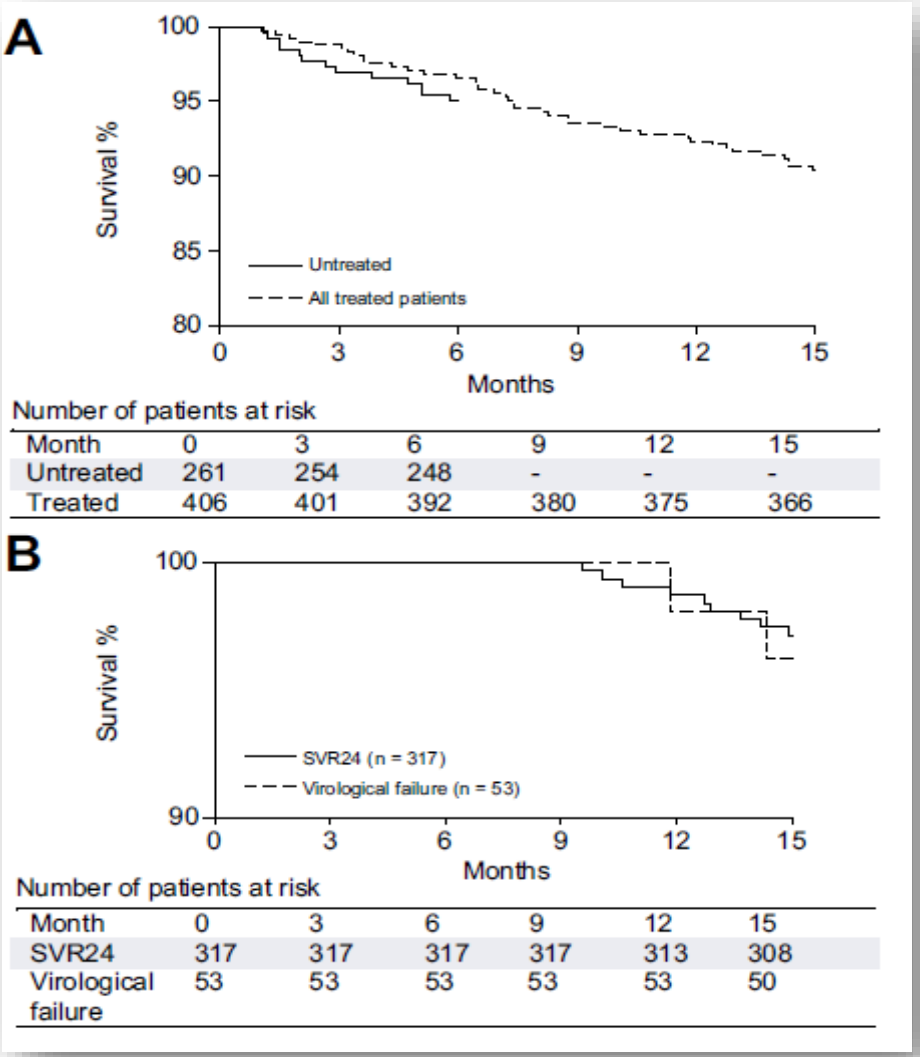
All colleagues participating in the PITER study and a special thanks to:

- the steamroller LORETA KONDILI

and

- MARZIA MARGOTTI who coordinated the data collection in my group.

Outcome after DAA: DECOMPENSATED SUBJECTS



Number of patients at risk

Month	0	3	6	9	12	15
Untreated	261	254	248	-	-	-
Treated	406	401	392	380	375	366

Number of patients at risk

Month	0	3	6	9	12	15
SVR24	317	317	317	317	313	308
Virological failure	53	53	53	53	53	50

CHEUNG MCM et al, J Hepatol 2016

Long-term FU of F2/F3 Fibrosis after SVR in SOF-based clinical trials

Liver-related complications after SVR	**F2 N=1456**	**F3 N=838**
HCC, n Exposure-adjusted incidence rate/100 p-y	2 0.06	5 0.25
Liver related events (Ascites/Varices/Encephalopathy/Jaundice)	7	21
Deaths	4	5
HCV relapse, n	0	1
HCV re-infection, n	4	2

ZEUZEM et al., EASL 2018