The Impact of DAA on HCC Occurrence

Professeur Didier Samuel

Centre Hépatobiliaire

Inserm-Paris Sud Research Unit 1193

Departement Hospitalo Universitaire Hepatinov

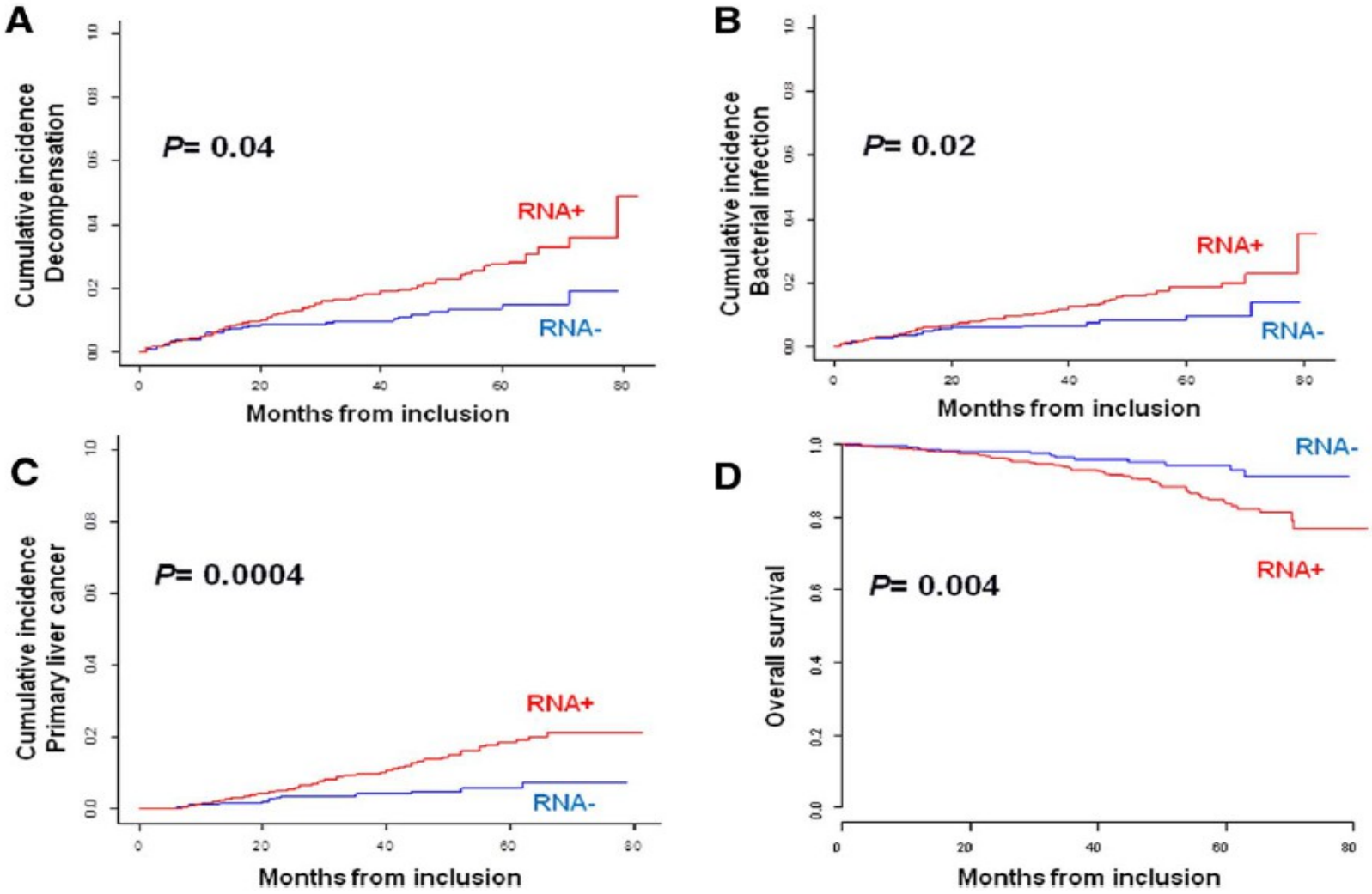
Hôpital Paul Brousse

Université Paris Sud

Villejuif, France

PHC 2018 - www.aphc.info

Impact of HCV Replication on Complications
Cirvir Cohort, 1308 HCV Cirrhosis



Trinchet JC Hepatology 2015

INTRODUCTION

- Annual incidence of HCC in untreated HCV cirrhosis is 3-7%
- Multiple studies have reported that patients who achieved SVR after IFN-based therapy showed:
  - Improvement in liver fibrosis
  - Decreased risk of liver-related complications
  - Decreased liver-related and overall mortality
  - Decreased risk of de novo HCC

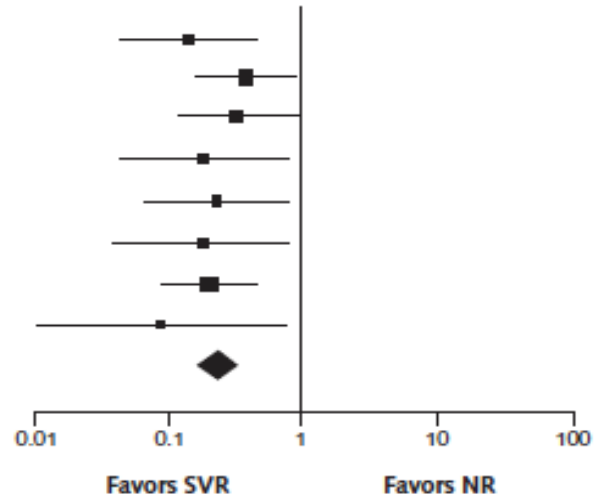
IFN-induced SVR reduce the risk of de novo HCC: meta-analysis

Figure 2. **Forest plot of adjusted hazard effects in persons with advanced liver disease.**

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Braks et al, 2007 (37)	−1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	−0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	−1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	−1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	−1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	−1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	−1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	−2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$

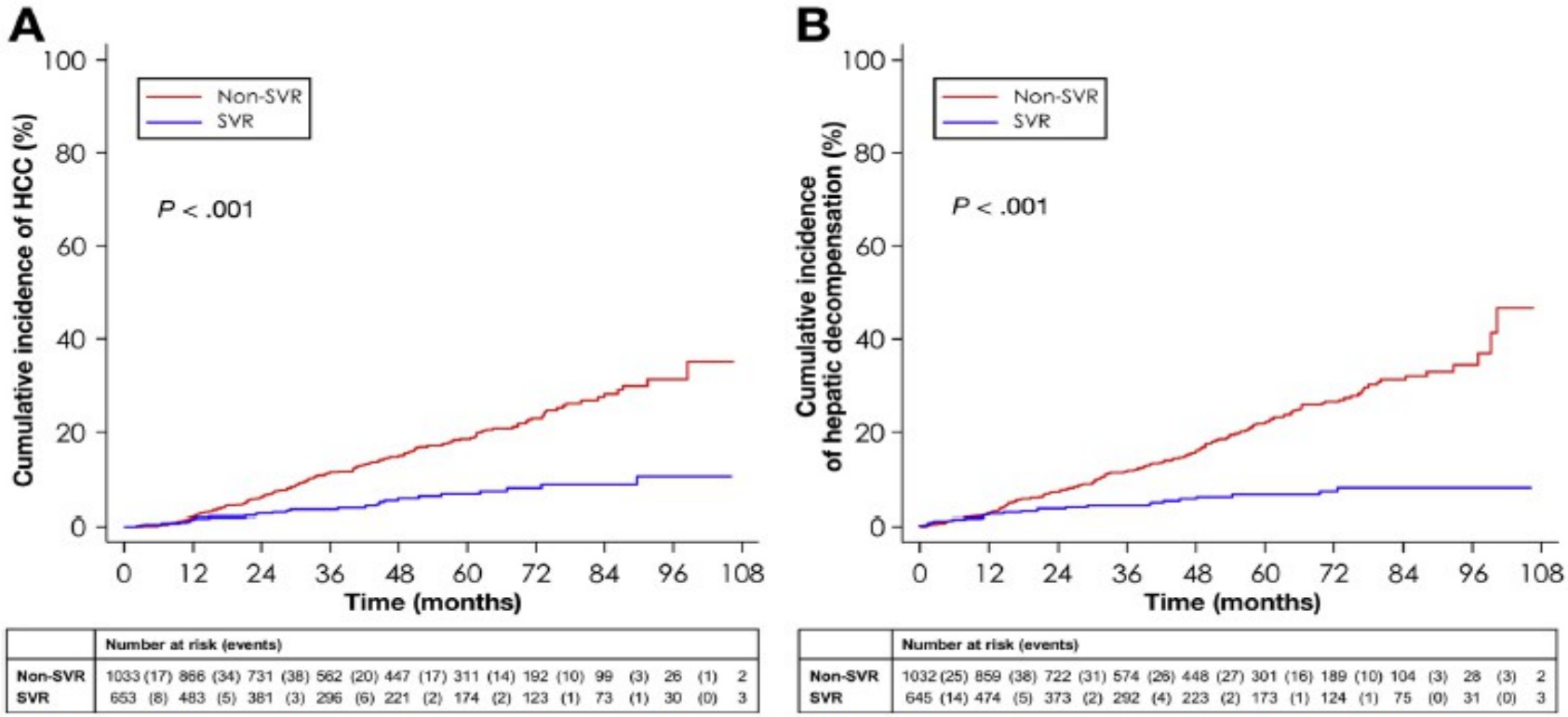


IV = inverse variance; NR = nonresponse; SVR = sustained virologic response.

Meta-analysis of 2649 patients with advanced liver disease found that SVR was associated with a reduction in the risk of HCC. Hazard ratio 0.23 (95% CI, 0.16 to 0.35); p<0.001

Morgan RL et al. Ann Intern Med 2013;158:329-337

IFN-induced SVR reduce the risk of de novo HCC and hepatic decompensation: prospective study



	Number at risk (events)																					
Non-SVR	1033	(17)	866	(34)	731	(38)	562	(20)	447	(17)	311	(14)	192	(10)	99	(3)	26	(1)	2
SVR	653	(8)	483	(5)	381	(3)	296	(6)	221	(2)	174	(2)	123	(1)	73	(1)	30	(0)	3

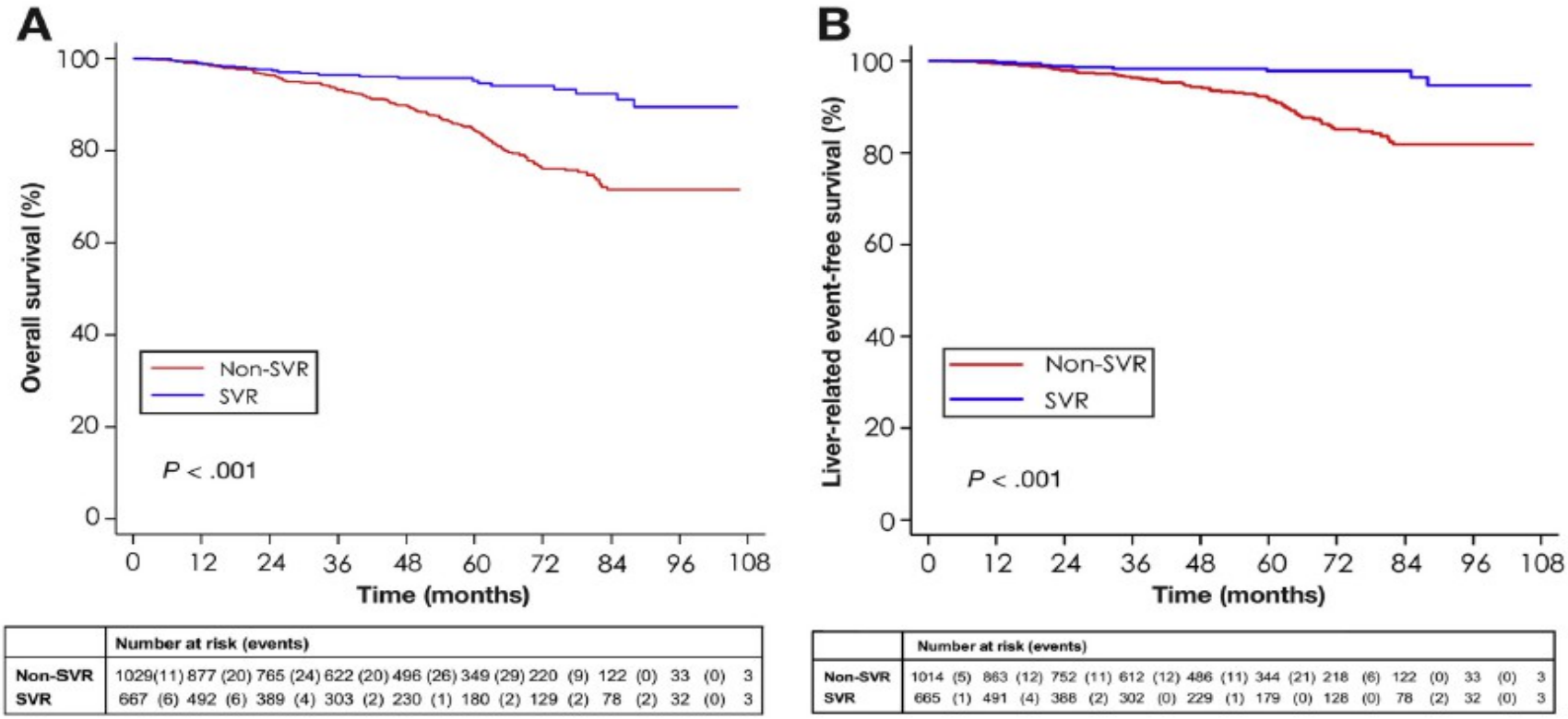
	Number at risk (events)																					
Non-SVR	1032	(25)	859	(38)	722	(31)	574	(26)	448	(27)	301	(16)	189	(10)	104	(3)	28	(3)	2
SVR	645	(14)	474	(5)	373	(2)	292	(4)	223	(2)	173	(1)	124	(1)	75	(0)	31	(0)	3

Figure 1. Incidence of liver complications according to SVR. (*A*) HCC (5-year CumI, 18.5% vs 6.7%; HR, 0.28; 95% CI, 0.19–0.43; $P < .001$). (*B*) Hepatic decompensation (5-year CumI, 22.0% vs 6.5%; HR, 0.26; 95% CI, 0.17–0.39; $P < .001$).

Prospective cohort including 1323 Child-Pugh A cirrhosis, median follow-up 58.2 months. All patients received antiviral therapy (mainly IFN)

Nahon P et al. Gastroenterology 2017;152:142-156

IFN-induced SVR reduce liver-related and overall mortality: prospective study



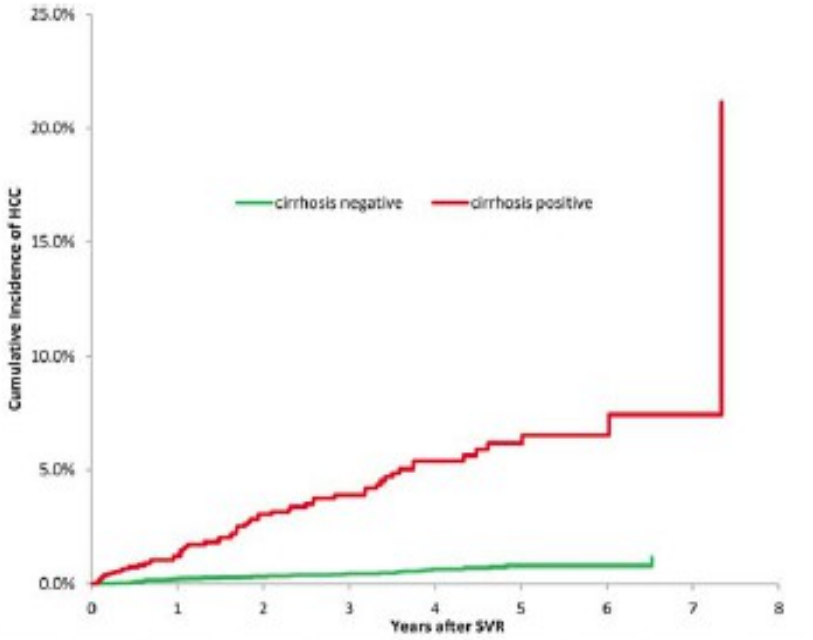
	Number at risk (events)
Non-SVR	1029(11) 877 (20) 765 (24) 622 (20) 496 (26) 349 (29) 220 (9) 122 (0) 33 (0) 3
SVR	667 (6) 492 (6) 389 (4) 303 (2) 230 (1) 180 (2) 129 (2) 78 (2) 32 (0) 3

	Number at risk (events)
Non-SVR	1014 (5) 863 (12) 752 (11) 612 (12) 486 (11) 344 (21) 218 (6) 122 (0) 33 (0) 3
SVR	665 (1) 491 (4) 388 (2) 302 (0) 229 (1) 179 (0) 128 (0) 78 (2) 32 (0) 3

Prospective cohort including 1323 patients with Child-Pugh A cirrhosis, median follow-up 58.2 months. All patients received antiviral therapy (mainly IFN)

Nahon P et al. Gastroenterology 2017;152:142-156

IFN-induced SVR reduce the risk of de novo HCC : retrospective study



Cirrhosis neg	at risk	9190	7167	5618	4199	2851	1609	566	73
	HCC	18	7	6	7	3	0	1	0
Cirrhosis pos	at risk	1548	1145	875	643	433	247	95	12
	HCC	17	19	7	9	3	1	1	1

FIG. 2. Cumulative incidence of HCC among patients with HCV who achieved SVR, stratified by the presence or absence of cirrhosis at the time of SVR. Gray's log-rank test, $P < 0.0001$.

- Retrospective study from the Veterans affairs HCV registry
- 10817 patients achieved IFN-induced SVR
- Overall HCC incidence rate 0.33% per year

El-Serag HB et al. Hepatology 2016;64:130-137

IFN-induced SVR reduce the risk of de novo HCC: retrospective study

TABLE 3. Predictors of HCC in Veterans With HCV Who Achieved an SVR

Variable	Level	HR (95% CI)	*P* Value
Diabetes (time-varying)	No	1.0 (ref)	
	Yes	1.876 (1.211-2.906)	0.0048
Race	White	1.0 (ref)	
	Black	1.398 (0.730-2.679)	0.3121
	Hispanic	2.269 (1.073-4.798)	0.0319
	Asian	3.016 (0.411-22.138)	0.2777
	Other	1.684 (0.231-12.248)	0.6069
	Missing	1.301 (0.716-2.362)	0.3875
Cirrhosis at SVR	No	1.0 (ref)	
	Yes	6.686 (4.319-10.350)	<0.0001
Alcohol	No	1.0 (ref)	
	Yes	1.676 (1.082-2.595)	0.0207
Age at SVR	<45	0.559 (0.133-2.345)	0.4269
	45-54	1.0 (ref)	
	55-64	2.043 (1.292-3.231)	0.0023
	65+	4.509 (1.955-10.400)	0.0004
HCV genotype	1	1.0 (ref)	
	2	0.591 (0.324-1.077)	0.0859
	3	1.620 (0.960-2.734)	0.0709

Results from Cox's proportional hazards model while adjusting for the competing risk of death.

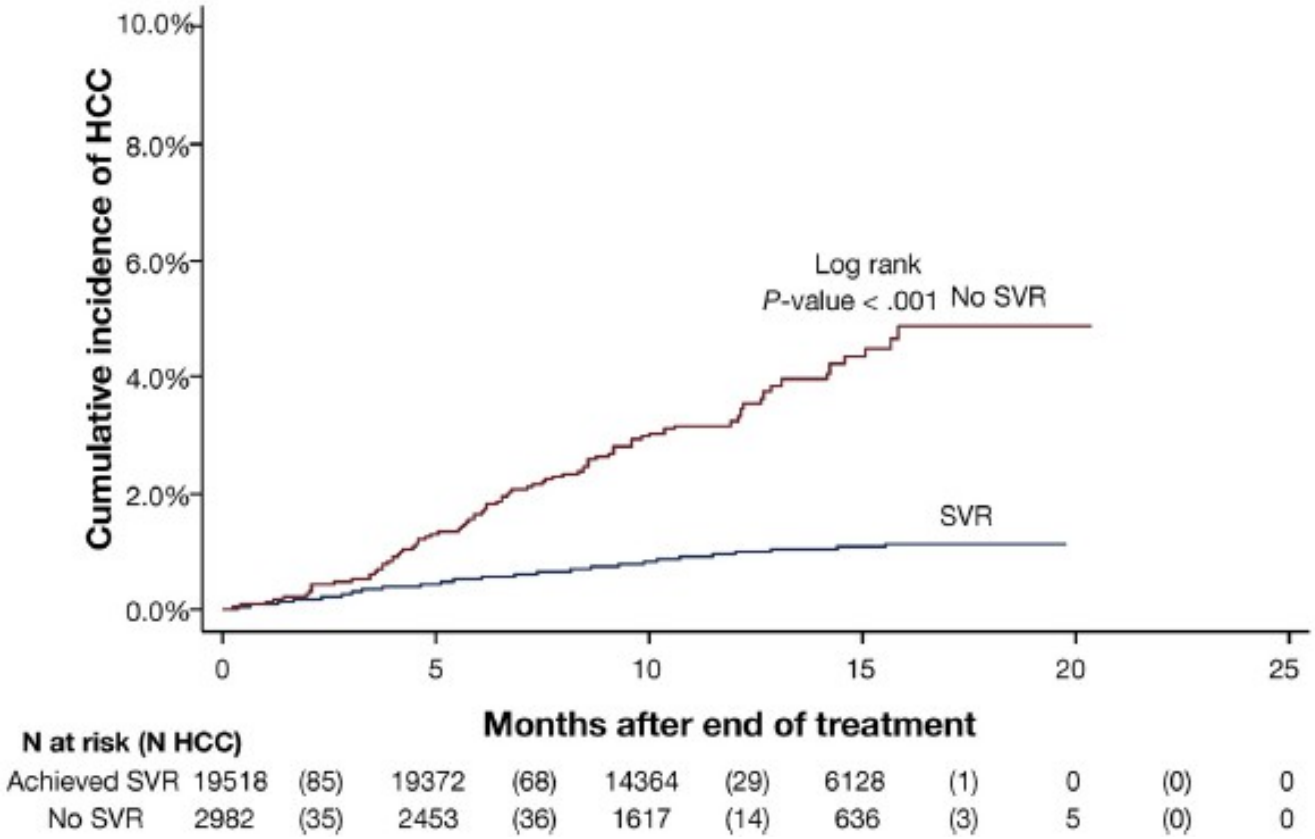
Predictors of HCC in patients who achieved SVR:

- Cirrhosis
- Diabetes
- Age > 64
- Genotype 3

El-Serag HB et al. Hepatology 2016;64:130-137

RISK OF DE NOVO HCC AFTER DAA THERAPY

STUDIES EVALUATING RISK OF DE NOVO HCC AFTER DAA THERAPY: Retrospective study



DAA-induced SVR is associated with a 76% reduction in HCC risk

22500 patients from Veterans health administration hospitals treated with DAA (19518 with SVR, 2982 without SVR). Cirrhosis 39%. Patients achieving SVR had a signif cantly reduced risk of HCC: 0.90 vs 3.45 HCC/100 person-years (HR, 0.28, 95% CI=0.22-0.36). Patients with cirrhosis had the highest annual incidence of HCC after SVR: 1.82 vs 0.34/100 person-years in patients without cirrhosis (HR, 4.73, 95% CI=3.34-6.68)

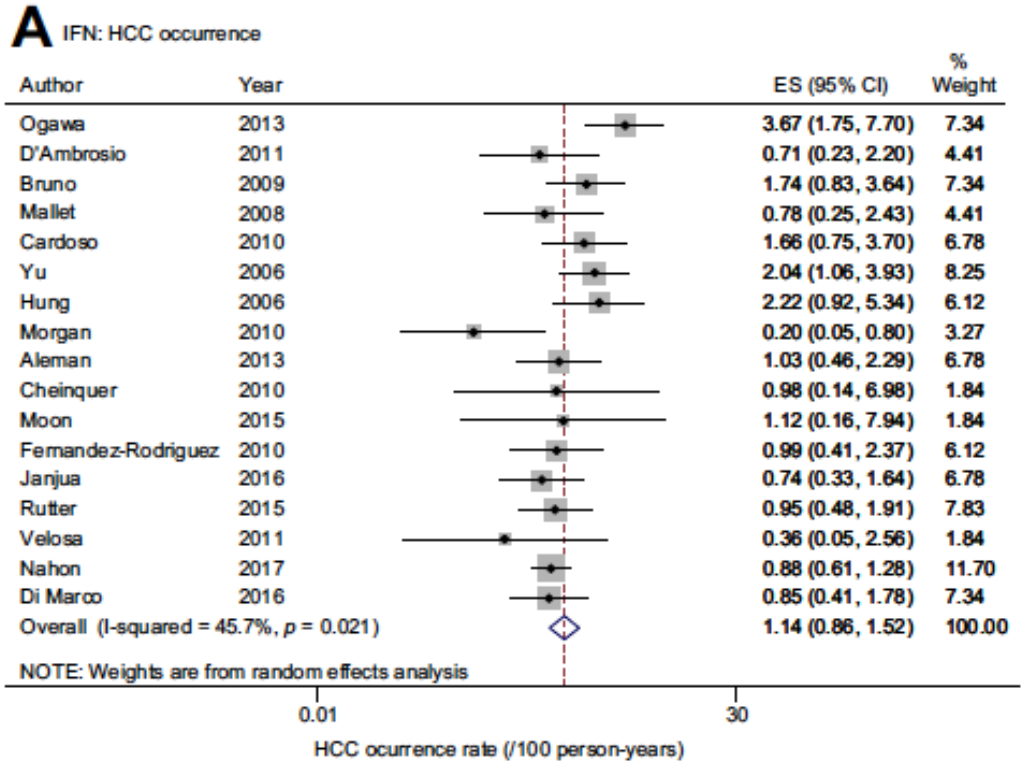
Kanwal F, Gastroenterology 2017;153:996-1005

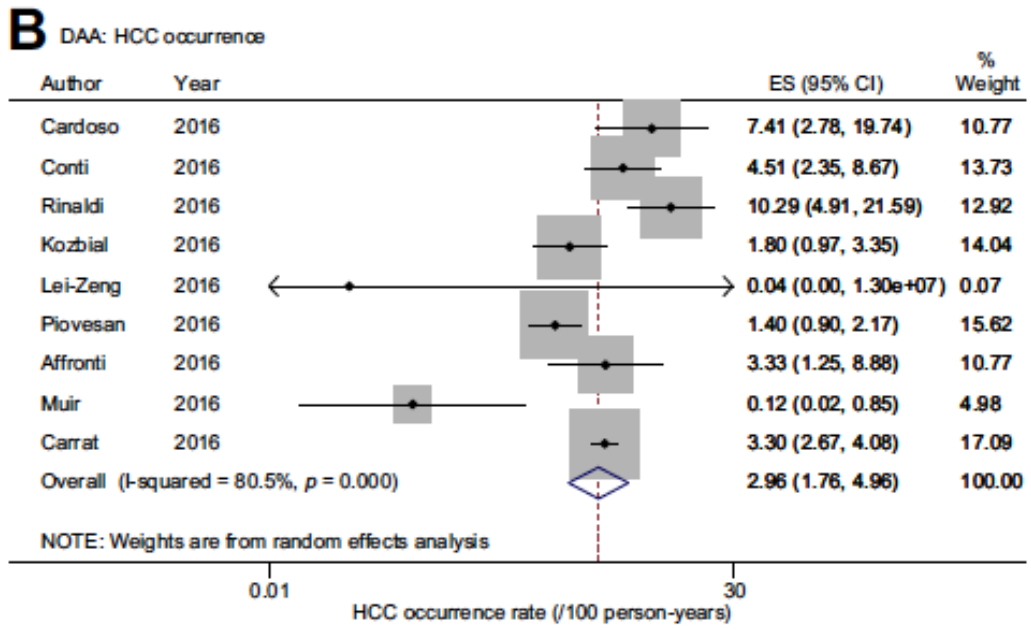
STUDIES EVALUATING RISK OF DE NOVO HCC AFTER DAA THERAPY

Authors	Type of study	n	Cirrhosis (%)	Follow-up (Median)	HCC incidence (%)
Cardoso	Retrospective	54	100%	12 months after SVR	7.4%
Kozbial	Retrospective	195	NA	13 months after DAA cessation	6.6%
Ravi	Retrospective	66	100%	6 months after DAA cessation	9.1%
Foster	Prospective	467	77.5%	6 months after DAA initiation	5.4%
Conti	Retrospective	285	100%	6 months after DAA cessation	3.16%
Cheung	Prospective	406	100%	15 months after DAA initiation	4% at 6 months (same as in 261 patients not receiving DAA) 6.7% at 1 year
Calleja	Retrospective	3233	52%	18 months after DAA initiation	0.9%
Kobayashi	Retrospective	77	NA	4 years	2.6%
Toyoda	NA	413	NA	NA	Annual incidence: 0.62-0.85%
Kanwal	Retrospective	22,500	39%		SVR: 0.9 per 100 patient-years No-SVR: 3.45 per 100 patient-years
Ioannou	Retrospective	21,948	24%	6.1 years	1.32 per 100 patient-years

Cardoso H, J Hepatol 2016; Kozbial K, J Hepatol 2016; Ravi S, Gastroenterology 2017; Foster GR, J Hepatol 2016; Conti F, J Hepatol 2016; Cheung MC, J Hepatol 2016; Calleja JL, J Hepatol 2017; Kobayashi M, J Med Virol 2017; Toyoda H, J Viral Hepat 2017; Kanwal F, Gastroenterology 2017; Ioannou GN, J Hepatol 2017

STUDIES EVALUATING RISK OF DE NOVO HCC AFTER DAA THERAPY: meta-analysis

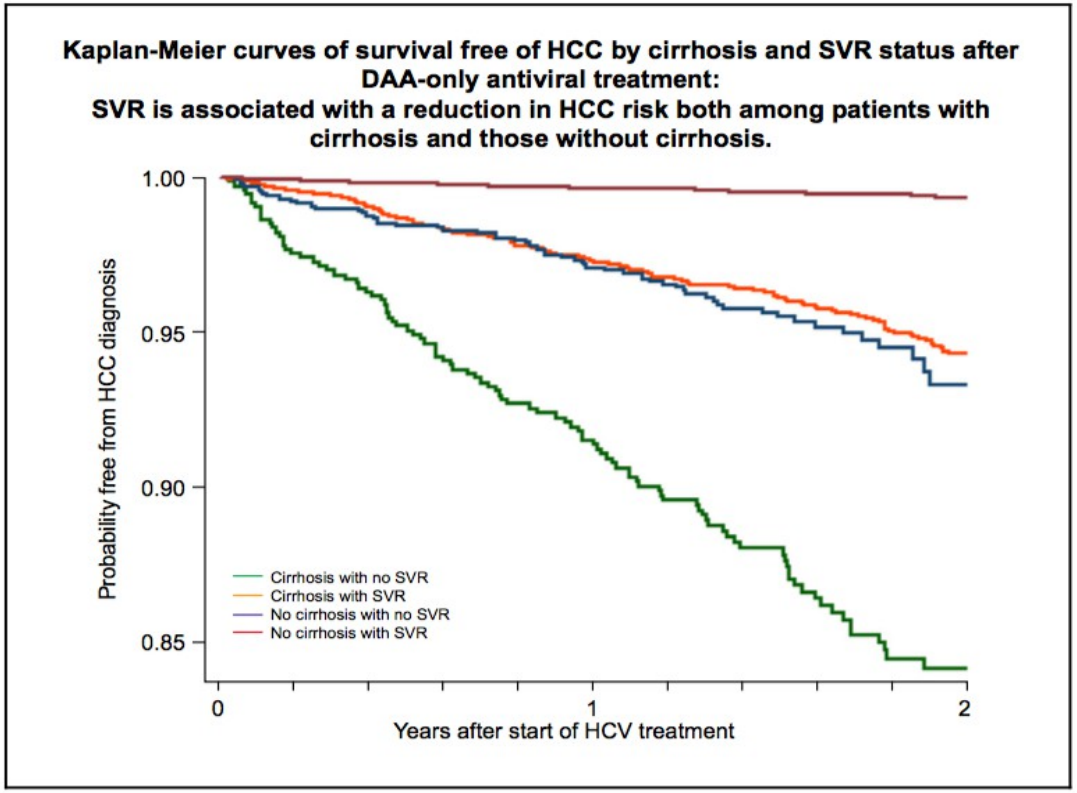




Meta-analysis: 26 studies from 2006 to 2017, IFN=17, DAA=9; prospective=19, retrospective=7
In meta-regression adjusting for study follow-up and age, DAA therapy was not associated with higher HCC occurrence risk following SVR

Waziry R, J Hepatol 2017;67:1204-1212

STUDIES EVALUATING RISK OF DE NOVO HCC AFTER DAA THERAPY: Retrospective study



DAA-induced SVR is associated with a 71% reduction in HCC risk

62354 patients receiving antiviral therapy in the Veterans affairs national healthcare system including 35871 (58%) treated with IFN, 4535 (7%) treated with IFN + DAA and 21948 (35%) treated with DAA. SVR was associated with a decreased risk of HCC whatever the antiviral regimen. DAA regimen was not associated with an increased risk of HCC compared to IFN regimen

Ioannou GN, J Hepatol 2018;68:25-32

RISK OF HCC RECURRENCE AFTER DAA THERAPY

- In the control group of the STORM study, the incidence of HCC recurrence following resection or ablation of HCC was around 20% at 6 months

- No adjuvant therapy including IFN has been shown to have a clinical benefit on the prevention of HCC recurrence following curative therapy for early HCC

- No recommendations for adjuvant therapies in clinical practice guidelines

DAA and HCC Recurrence?

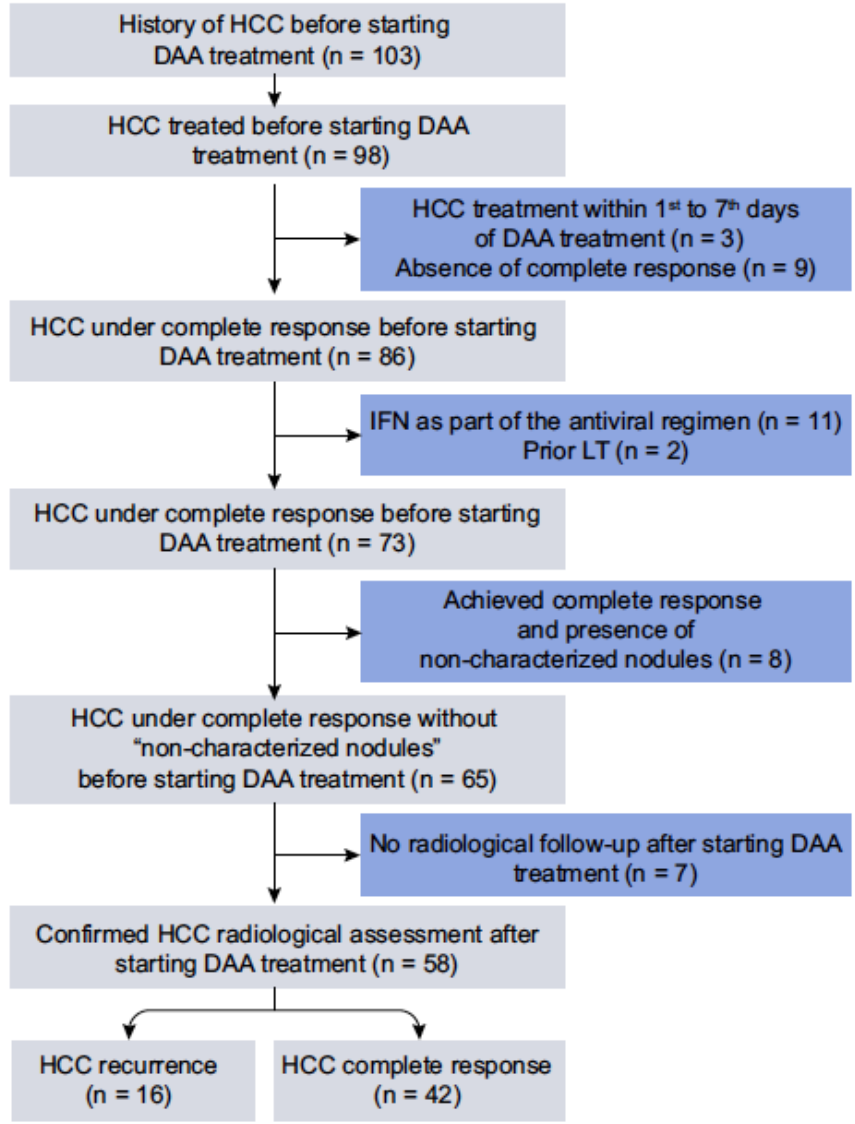


Fig. 1. Flowchart of the study.

Reig J Hepatol 2016

DAA and HCC Recurrence?

Table 2. Liver function and tumor-related variables of patients with HCC recurrence at the three relevant time points of the study.

	At time of HCC treatment			At time of starting DAA		At time of HCC recurrence after DAA	
Patient	PS	Child-Pugh	BCLC	PS	Child-Pugh	PS	Child-Pugh
1	0	5	A (one nodule)	0	5	0	5
2	0	6	A (one nodule)	0	8	2	8
3	0	6	0	0	5	0	5
4	0	6	A (one nodule)	0	5	0	6
6	0	n.a.*	A (one nodule)	0	n.a.*	0	n.a.*
7	0	5	A (one nodule)	0	5	0	5
8	0	6	A (≤3 nodules and ≤3 cm)	0	6	0	6
9	0	5	A (one nodule)	0	5	0	5
10	0	6	A (one nodule)	0	6	0	5
11	0	5	A (one nodule)	0	5	0	5
12	0	5	A (≤3 nodules and ≤3 cm)	0	5	0	5
13	0	5	A (one nodule)	0	5	0	5
14	0	5	0	0	7	3	7
15	0	7	A (one nodule)	0	10	0	12
16	0	6	0	0	6	0	6

Reig J Hepatol 2016

DAA and HCC Recurrence?

Table 3. Baseline characteristics and outcome of the 16 patients with hepatocellular recurrence.

Patient	Treatment of HCC before DAA	Risk profile at pathology*	At time of starting DAA		At the time of HCC recurrence		HCC treatment	Status at the end of follow-up
			BCLC	AFP (ng/dl)	Pattern of progression	AFP (ng/dl)		
1	Resection	Low risk	A	91	NIH (one nodule)	912	Resection	Alive
2	Resection	Low risk	A	18	NIH (multinodular)	42	BSC	Dead
3	Resection	Low risk	0	2.3	NIH (one nodule)	1271	Resection	Alive
4	Resection	Low risk	A	12	NIH (≤3 nodules ≤3 cm)	5	Ablation	Alive
5	Resection	Low risk	A	4.2	NIH (≤3 nodules ≤3 cm)	2.1	OLT	Alive
6	Resection	High risk	A	1	NIH (one nodule)	112	Ablation	Alive
7	Resection	High risk	A	8	NIH (one nodule)	6	OLT	Alive
8	Ablation	n.a.	A	38	NIH (infiltrative) + NEH**	21,184	Sorafenib	Alive
9	Ablation	n.a.	A	66.2	IHG	7.9	Ablation	Alive
10	Ablation	n.a.	A	3	NIH (infiltrative) ***	n.a.	BSC	Alive
11	Ablation	n.a.	A	21.2	IHG	10.2	Ablation	Alive
12	Ablation	n.a.	A	6.7	NIH (one nodule)	3.8	OLT	Alive
13	Ablation	n.a.	A	14	IHG	5	Ablation	Alive
14	Ablation	n.a.	0	369	NIH (infiltrative) + NEH	n.a.	BSC	Alive
15	Ablation	n.a.	A	5	NIH (≤3 nodules ≤3 cm)	8	OLT	Alive
16	Ablation	n.a.	0	26	NIH (≤3 nodules ≤3 cm) ****	26	Ablation	Alive

Reig J Hepatol 2016

RISK OF HCC RECURRENCE AFTER DAA THERAPY: Prospective study

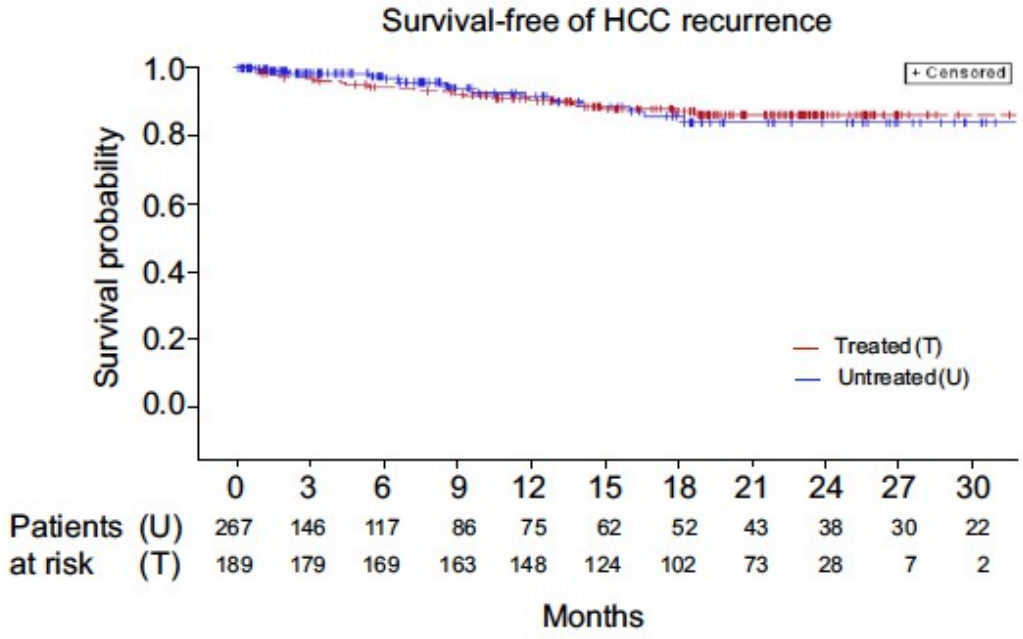


Fig. 2. Recurrence of HCC according to DAA treatment in the ANRS CO22 HEPATHER cohort. Pseudo-survival curves were plotted for time-dependent DAA treatment.

No increased risk of HCC recurrence after DAA treatment

ANRS CO22 HEPATHER cohort, 267 patients with a history of treated HCC, 189 patients received DAA

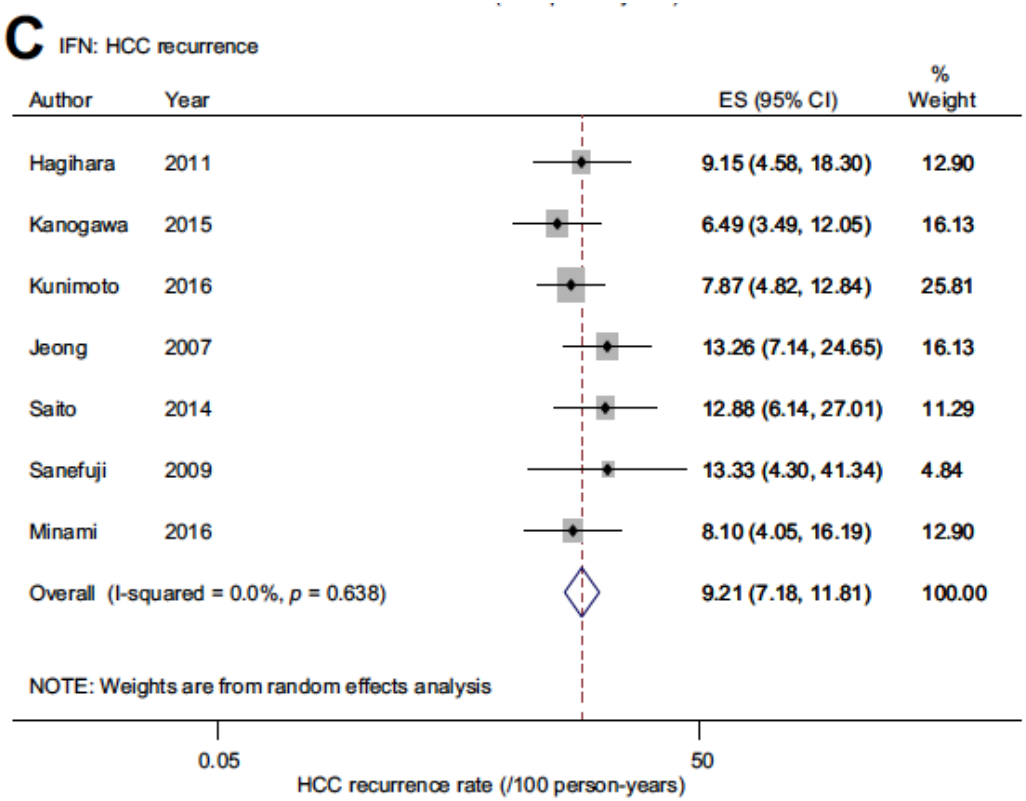
ANRS, J Hepatol 2016;65:734-740

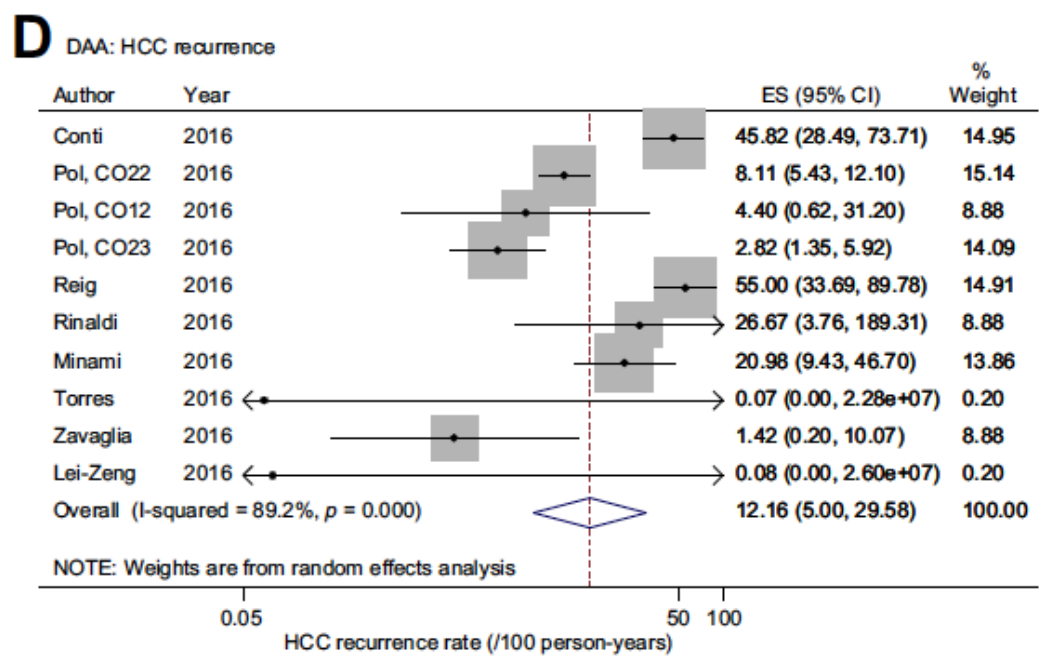
STUDIES EVALUATING RISK OF HCC RECURRENCE AFTER DAA THERAPY

Authors	Type of study	n	Treatment for previous HCC	Follow-up (Median)	HCC recurrence (%)
Reig	Retrospective	58	Resection, ablation, TACE	6 months from DAA initiation	27.6% Median 3.5 months from DAA initiation to HCC recurrence
Conti	Retrospective	59	Resection, ablation, TACE	12 months from HCC treatment to DAA initiation	28.8% Within 24 weeks of DAA completion
ANRS	Prospective	HEPATHER: 189/267 (71%) received DAA	Resection, ablation, LT	DAA treated: 20 months from DAA initiation DAA untreated: 26 months from SVR	DAA treated: 13% 0.73 per 100 person-months DAA untreated: 21% 0.66 per 100 person-months
		CirVir: 13/76 (17%) received DAA	Resection, ablation	21 months from SVR	DAA treated: 1.11 per 100 person-months DAA untreated: 1.73 per 100 person-months
		CUPILT: 314	LT	67 months (mean) from LT to DAA initiation	2.2%; 7 months (mean) from DAA initiation to HCC recurrence
Cabibbo	Prospective	143	Resection, ablation, TACE	2 months (mean) from HCC treatment to DAA initiation Follow-up 9 months after DAA initiation	12% within 6 months of DAA initiation 26.6% within 12 months of DAA initiation
Calleja	Retrospective	70	NA	20 months (mean) from HCC treatment	12.9% within 6 months of DAA initiation 30% within 12 months of DAA initiation
Minami	NA	27/926 (3%)	Ablation	16 months from DAA initiation	29.8% within 12 months of DAA initiation (vs. 31% in untreated patients)

Reig M, J Hepatol 2016; Conti F, J Hepatol 2016; ANRS, J Heatol 2016; Cabibbo G, Pharmacol Ther 2017; Calleja JL, J Hepatol 2017; Minami T, J Hepatol 2016

STUDIES EVALUATING RISK OF RECURRENT HCC AFTER DAA THERAPY: meta-analysis





Meta-analysis: 2352 patients, IFN=1485, DAA=867

In meta-regression adjusting for study follow-up and age, DAA therapy was not associated with higher HCC recurrence risk following SVR

Waziry R, J Hepatol 2017;67:1204-1212

CONCLUSIONS

- There is almost no risk of HCC in non-cirrhotic patients with SVR highlighting the need to treat HCV infection at early f brosis stage
- IFN- or DAA-induced SVR is associated with a decreased risk of HCC occurrence
- The risk of HCC persists in cirrhotic patients with SVR, therefore screening should be maintained
- As for IFN-based therapy, the impact of DAA-based therapy on prevention of HCC recurrence is debated and need further studies

Thanks

Medico Surgical Team at the Centre Hepatobiliaire
B. Roche
T. Antonini, A. Coilly, JC. Duclos-Vallée, E. De Martin , G Pelletier
R Sobesky, MG Tateo
P. Ichai, F Saliba, M Boudon, S André
D. Cherqui, D. Castaing, R Adam, A Sa Cunha, E Vibert,
O Ciaccio, G Pittau and all the team

Centre Hépato-Biliaire
HOPITAL PAUL BROUSSE