Cohort studies hepatitis C treatment

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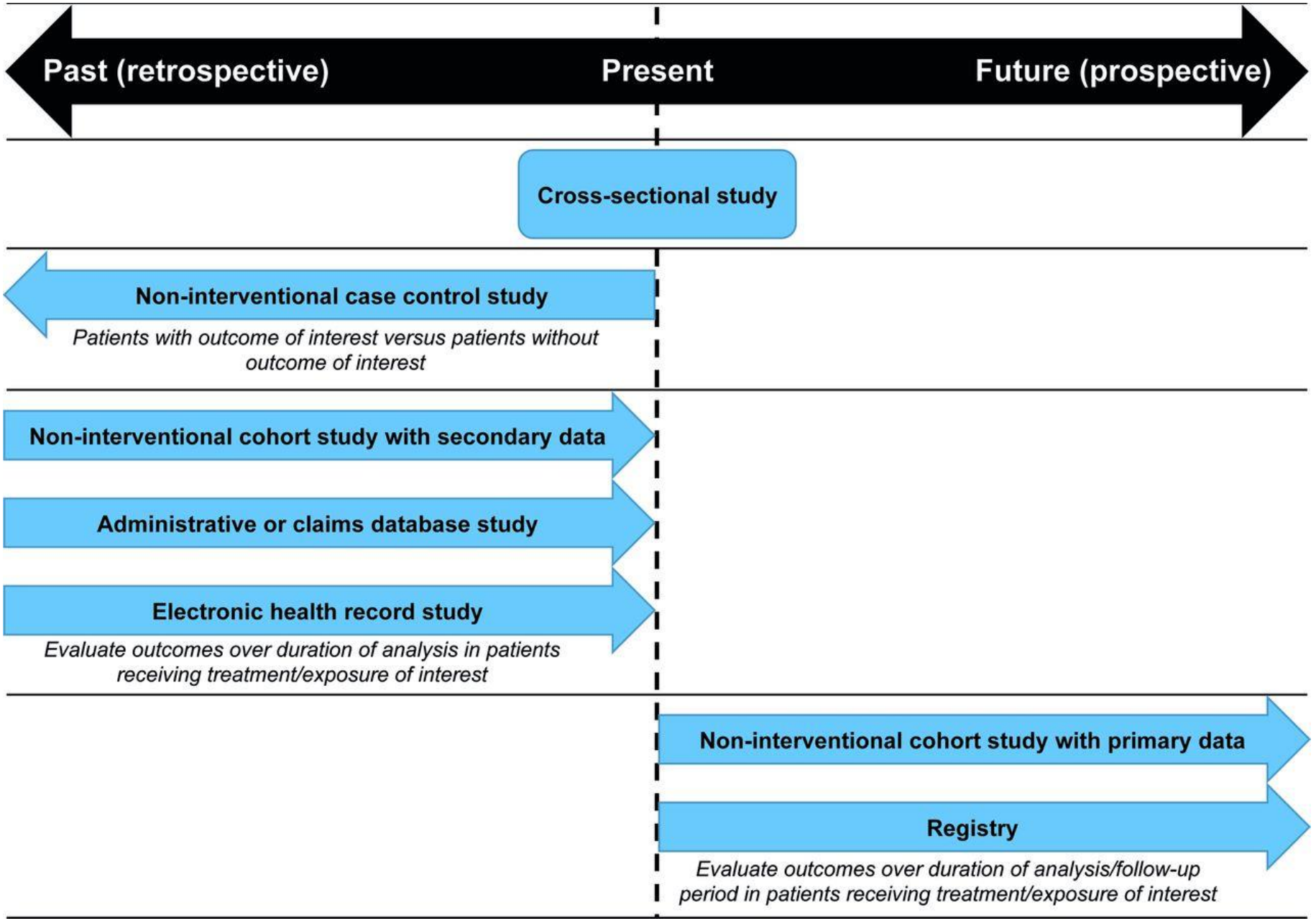
Types of cohort study



Outline

- Access to and impact of treatment
- Ethnic, geographic differences
- Outcomes of SVR
- Liver transplant
- Effect on comorbidities
- Hepatocellular carcinoma

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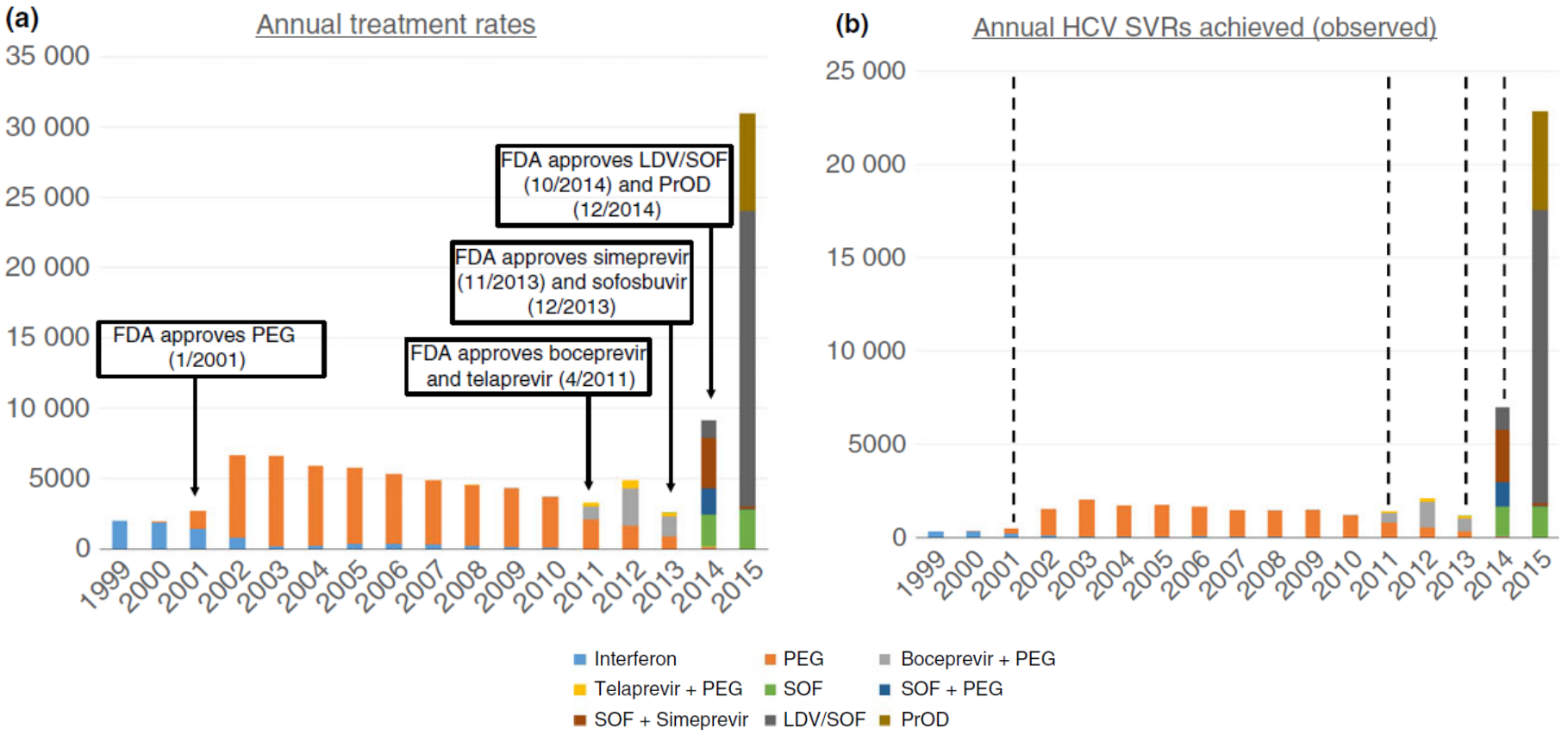
Annual hepatitis C virus regimens initiating and achieving sustained virological response

All treatments January 1999 to 31 December 2015 (n = 105 369 VA system)

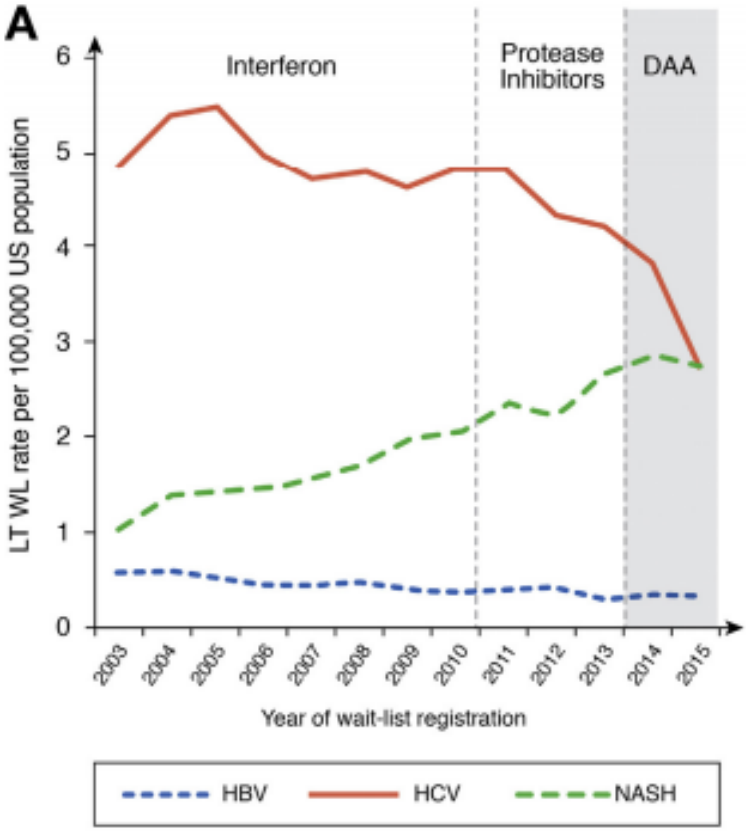
21-fold increase in the number of patients achieving HCV cure.



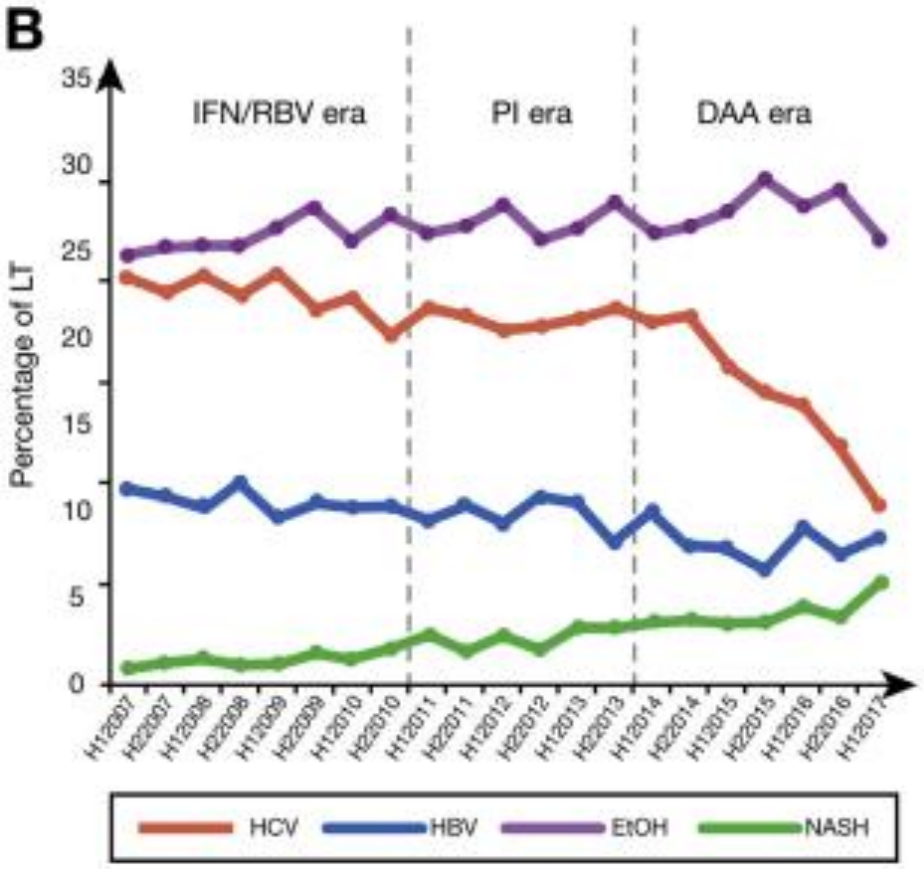
Moon, A. M., et al. (2017). Aliment Pharmacol Ther **45**(9): 1201-1212

Decline in the proportion of patients on liver transplant waitlists
United States and in Europe: public health population benefits

Etiology of cirrhosis hepatitis C since the introduction of DAAs



US Scientific Registry of Transplant Recipients
annually from 2003 through 2015



Data from the European Liver Transplant Registry
from January 2007 to June 2017

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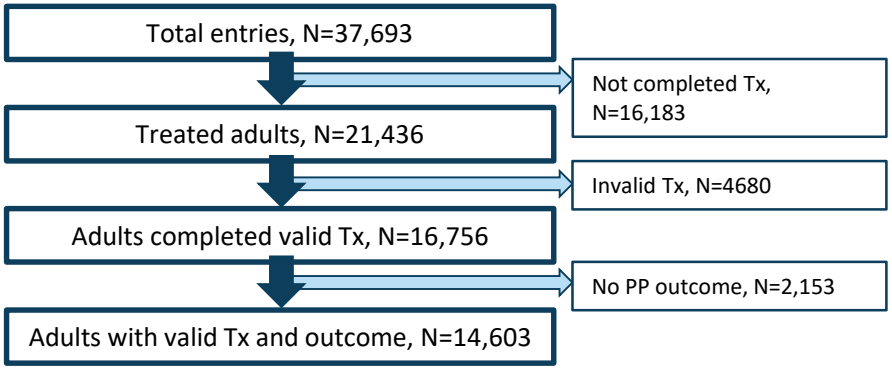
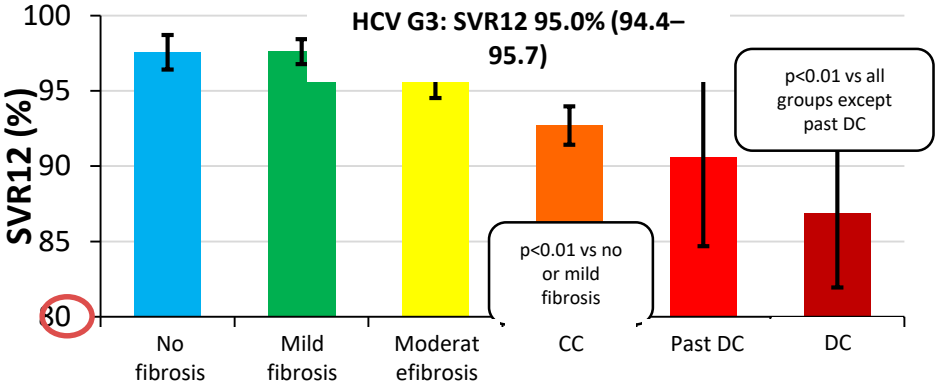
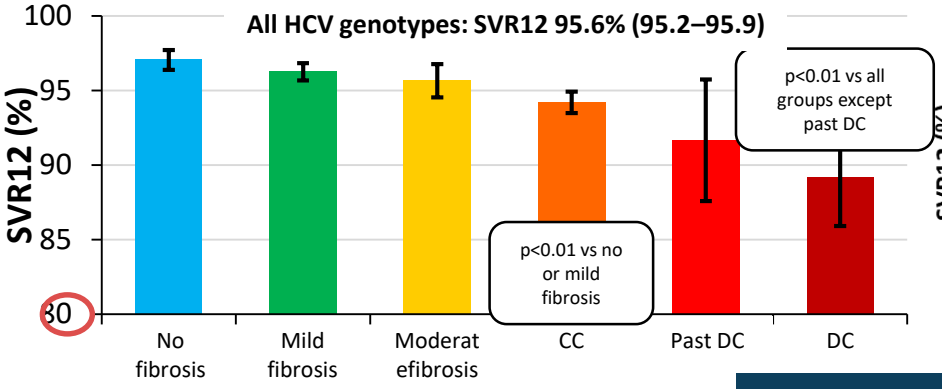
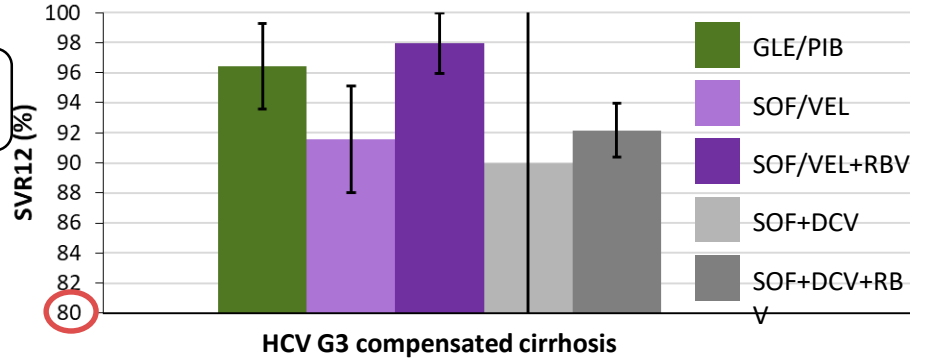
Effectiveness of therapy in 16,567 DAA-treated people in England: High response rates in HCV G3 infection regardless of degree of fibrosis, but RBV improves response in cirrhosis







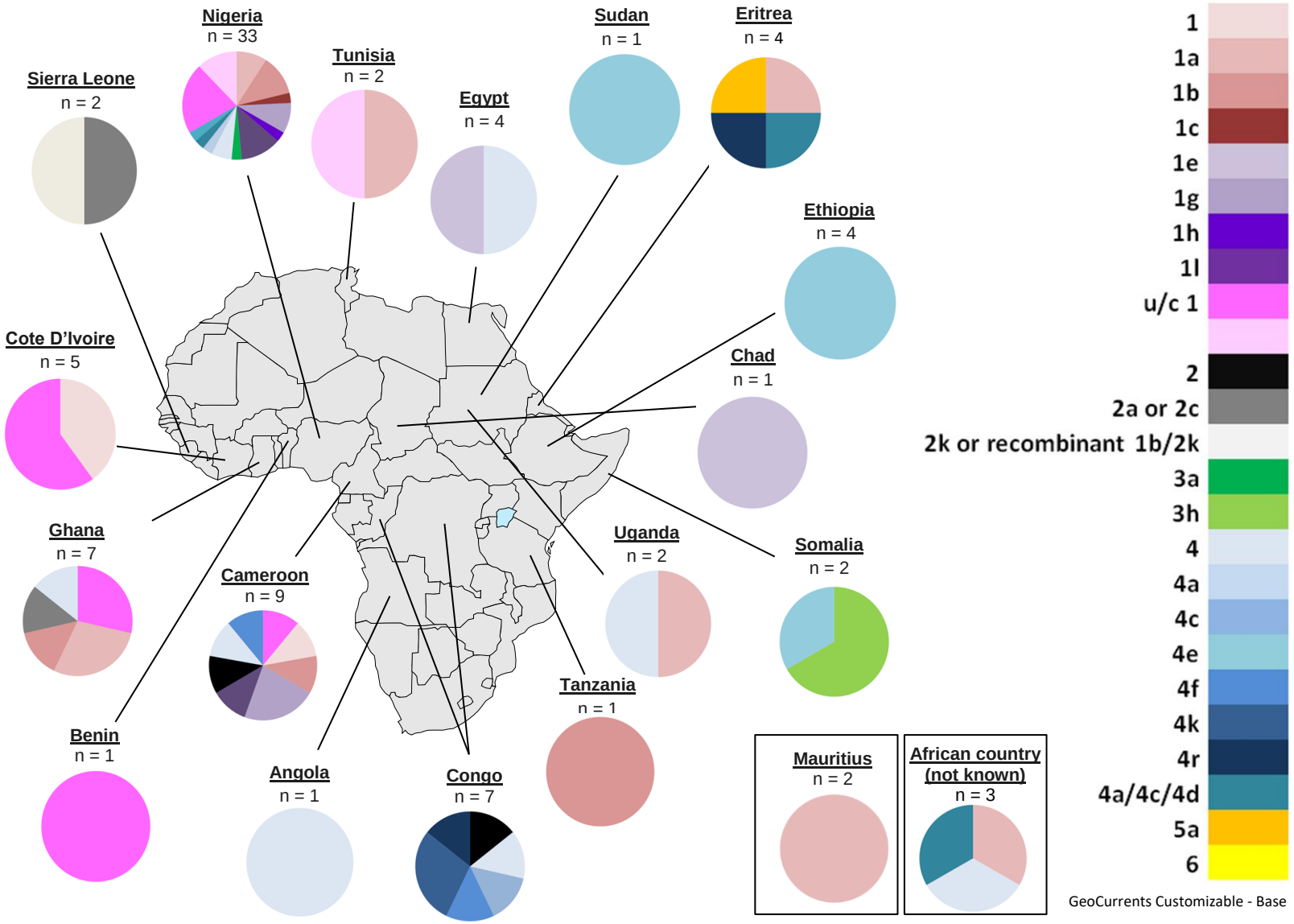


- HCV G3 response rates with GLE/PIB are excellent at all stages of fibrosis
- In HCV G3 compensated cirrhotics, SOF/VEL is improved by RBV

Drysdale K, et al. EASL 2019, Vienna, Austria. #LB-07

Subtypes African patients south London

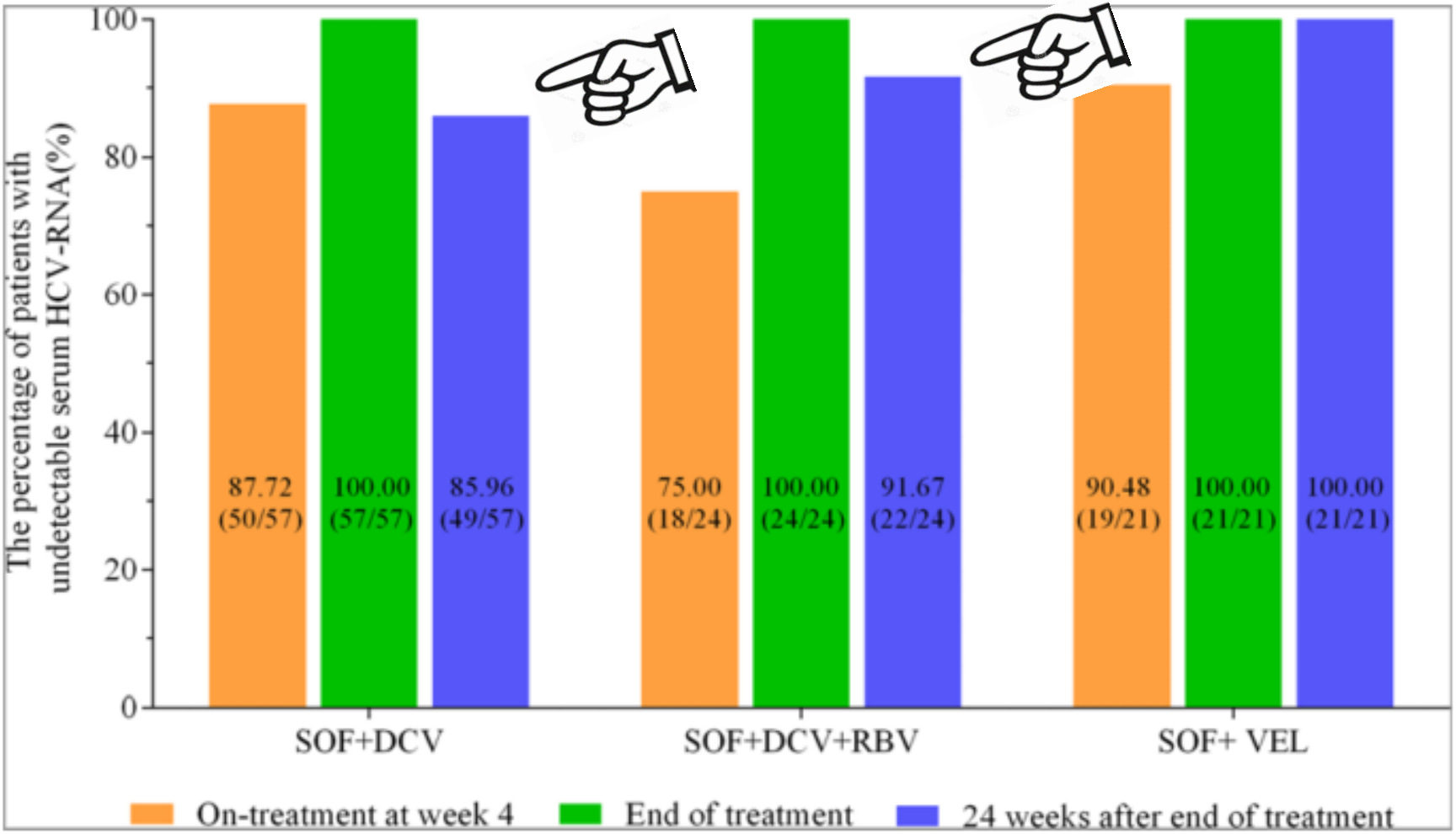
SVR rates suboptimal with non 1a and 1b and non 4a/4d and first gen NS5A inhibirors



Childs K et al submitted. EASL 2019

Efficacy of DAAs in Chinese HCV-GT3 patients

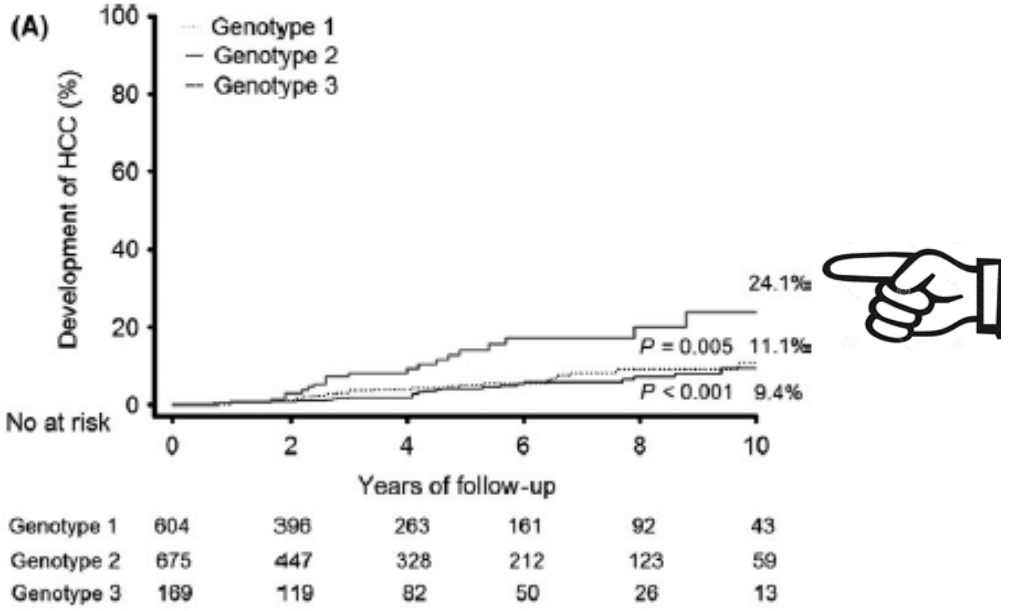
SOF-based regimens effective. SOF VEL higher response rates

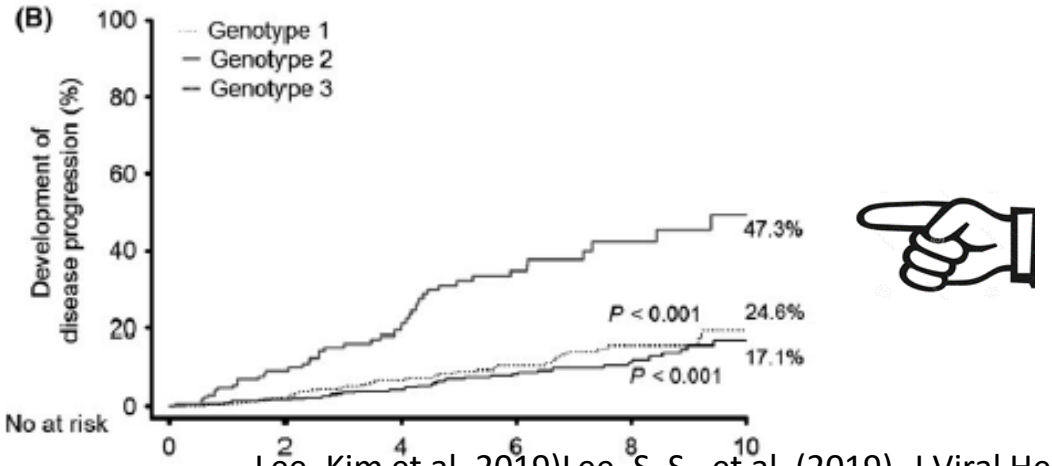


Tao, Y. C., et al. (2018). Virol J **15**(1): 150

The impact of genotype 3 and non-3 on HCC incidence and on disease progression in chronic HCV: Asian patients

n=1448 three Korean centres: 10-year cumulative occurrence rates of HCC and progression





Lee, Kim et al. 2019)Lee, S. S., et al. (2019). J Viral Hepat **26**(4): 459-465

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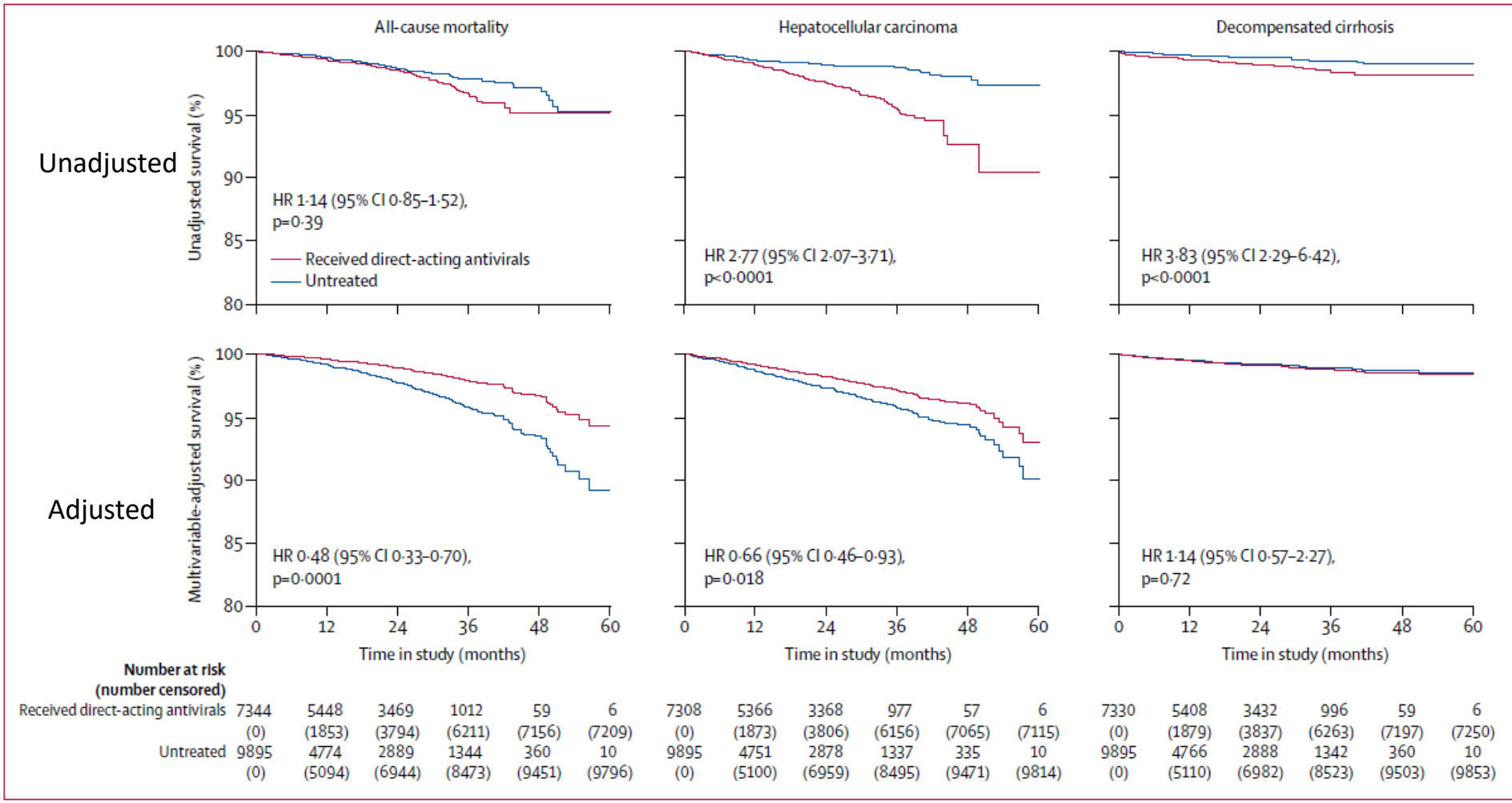
Incidence death, hepatocellular carcinoma, and decompensated cirrhosis between patients treated with direct-acting antivirals and those untreated: Cirrhosis

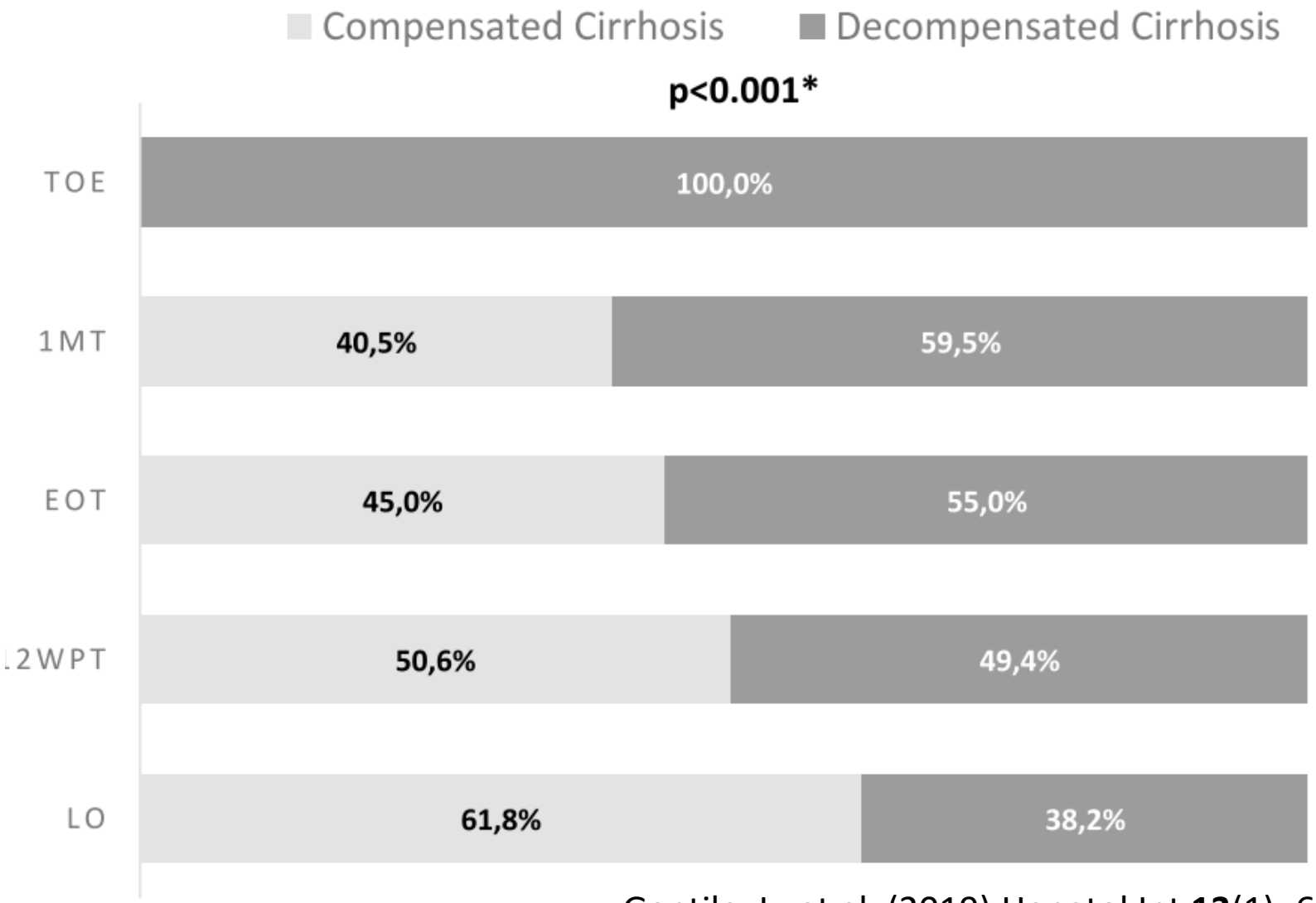
Observational cohort study French ANRS CO22 Hepather cohort: 2012 - 2015, 9895 included in analyses. Median follow-up 33.4 months Treatment DAA in 7344 patients, and 2551 UnRx



Carrat, F., et al. (2019). Lancet **393**(10179): 1453-1464.

Improvement in liver function and re-compensation

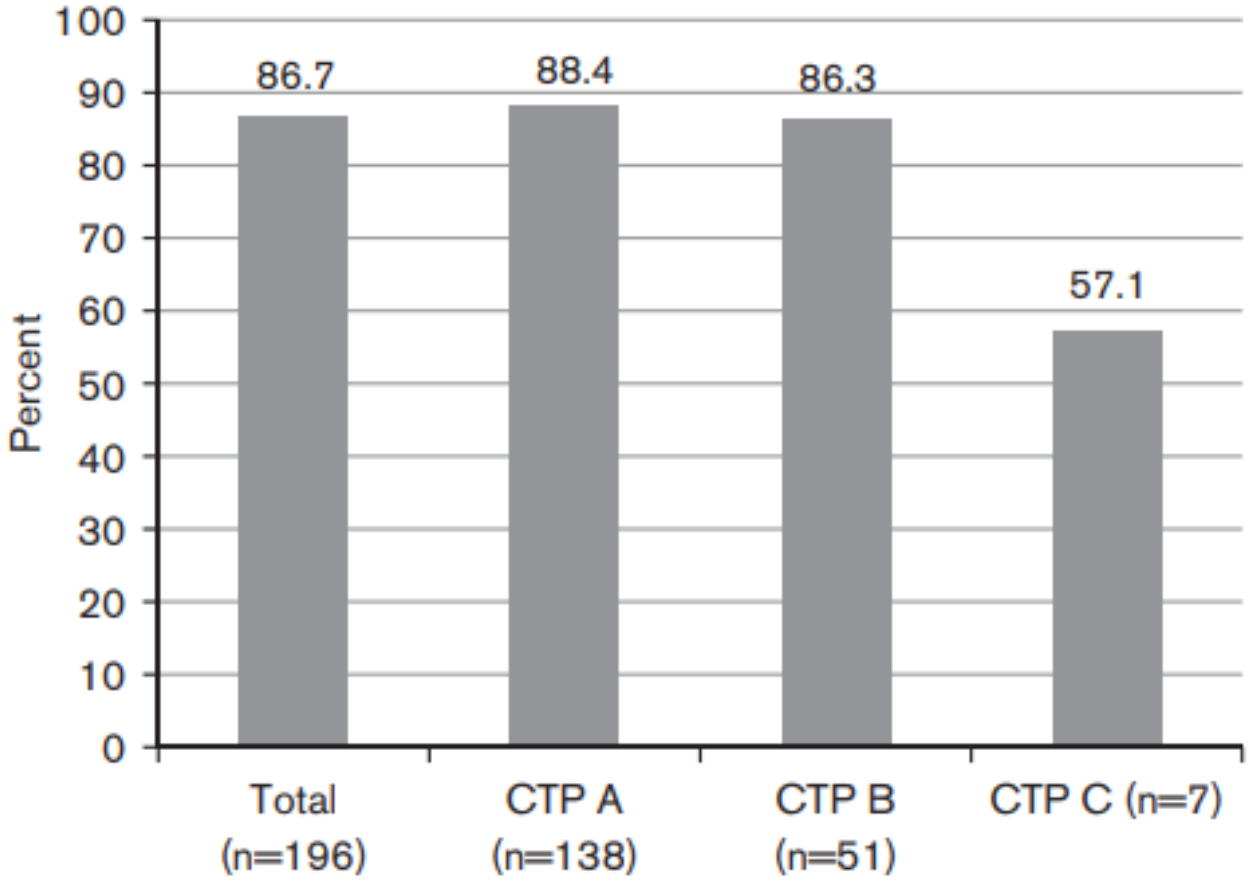
Prospective multicentre study among patients with **Child-Pugh B cirrhosis** of an Italian cohort (LINA cohort) (89) who received treatment with DAAs: status at different times of observation



Gentile, I., et al. (2019) Hepatol Int **13**(1): 66-74.

Treatment of hepatitis C with direct-acting antivirals reduces liver-related hospitalizations in patients with cirrhosis

Retrospective cohort analysis single US center: Compared patients HCV cirrhosis according to treatment/no treatment status: primary outcome was the difference in the incidence rate of liver-related hospitalizations



Hill, L. A., et al. (2018). Eur J Gastroenterol Hepatol **30**(11): 1378-1383.

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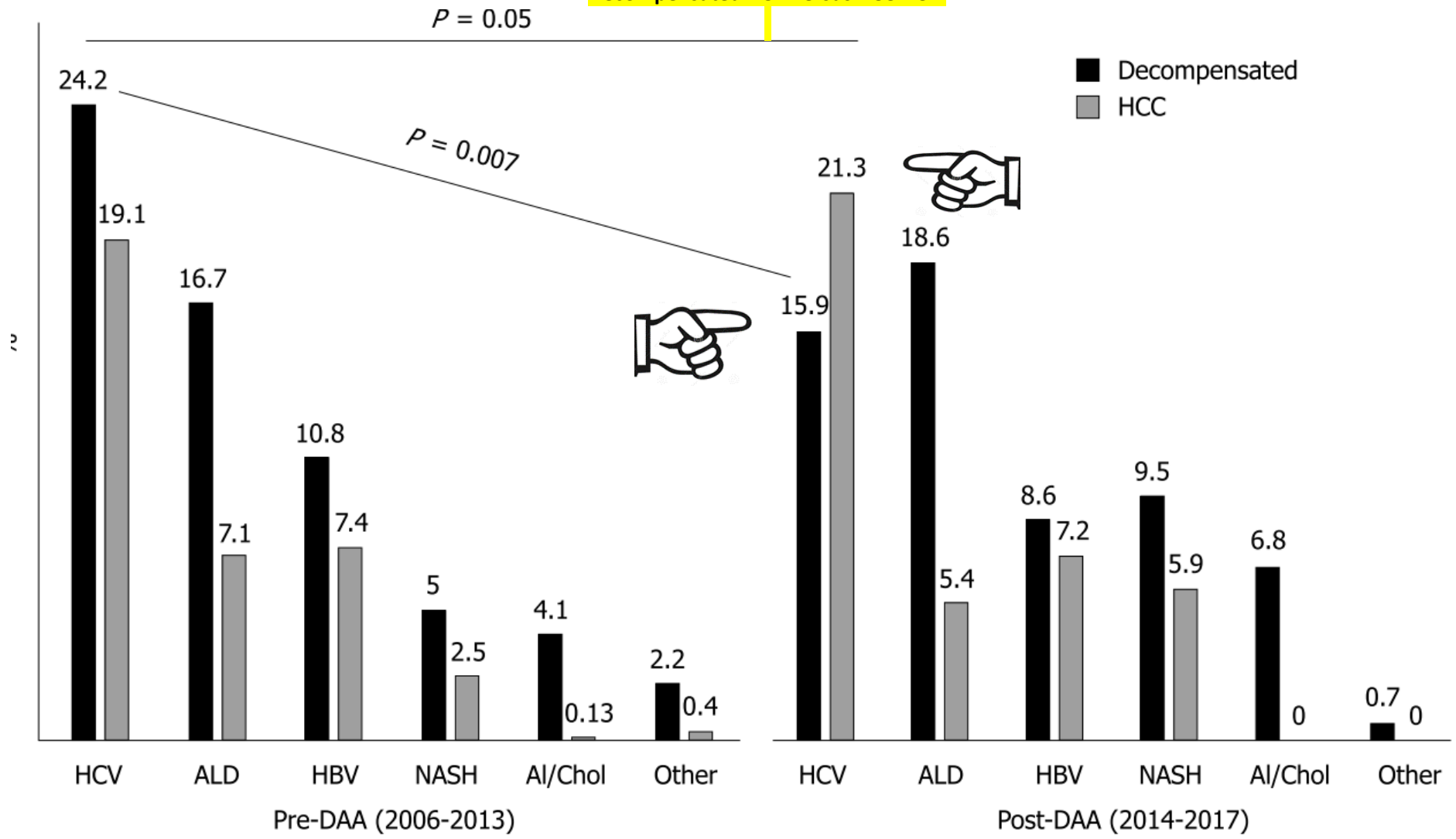
Trends in waiting list registration before and after direct-acting antiviral introduction.

Padua University Hospital. N= 1194 HCV-related cirrhosis main etiology WL registration

HCV-related cirrhosis significantly decreased as indication to WL registration after DAA introduction

Decompensated HCV versus HCC HCV



Ferrarese, A., et al. (2018). World J Gastroenterol **24**(38): 4403-4411.

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Impact of HCV eradication on HbA1c (%)

2,435 patients with diabetes who underwent DAAtreatment for HCV in the national VA system.

	Pretreatment HbA_{1c}	Post-treatment HbA_{1c}	Absolute change in HbA_{1c} (post-treatment from pretreatment)	Mean difference in HbA_{1c} drop in SVR vs. no SVR groups	*P* value	Adjusted* mean difference in HbA_{1c} drop in SVR vs. no SVR	*P* value
All patients							
No SVR	7.27 (1.6)	7.08 (1.5)	−0.19 (1.3)	−0.18	0.03	−0.13	0.1
SVR	7.20 (1.5)	6.82 (1.3)	−0.37 (1.2)				
Patients with pretreatment HbA_{1c} >7.2%							
No SVR	8.54 (1.2)	7.89 (1.6)	−0.65 (1.5)	−0.33	0.02	−0.34	0.02
SVR	8.54 (1.2)	7.56 (1.3)	−0.98 (1.4)				
Patients with pretreatment HbA_{1c} ≤7.2%							
No SVR	6.1 (0.7)	6.4 (1.06)	0.22 (0.9)	−0.15	0.04	−0.05	0.5
SVR	6.2 (0.6)	6.3 (0.9)	0.07 (0.8)				
Patients with cirrhosis							
No SVR	7.2 (1.5)	6.9 (1.4)	−0.27 (1.35)	−0.02	0.8	0.05	0.7
SVR	7.1 (1.5)	6.8 (1.3)	−0.30 (1.29)				
Patients without cirrhosis							
No SVR	7.4 (1.6)	7.3 (1.6)	−0.09 (1.3)	−0.33	0.005	−0.31	0.01
SVR	7.2 (1.4)	6.8 (1.2)	−0.42 (1.2)				

Values are reported as mean (SD) unless otherwise indicated. *Adjusted by multiple linear regression for age, sex, race/ethnicity, cirrhosis, platelet count, hemoglobin level, creatinine, bilirubin, albumin, INR, BMI, and FIB-4 score.

Future studies are needed to determine to assess long-term effect on complications of diabetes such as nephropathy, neuropathy, and cardiovascular disease

Hum, J., et al. (2017). Diabetes Care **40**(9): 1173-1180

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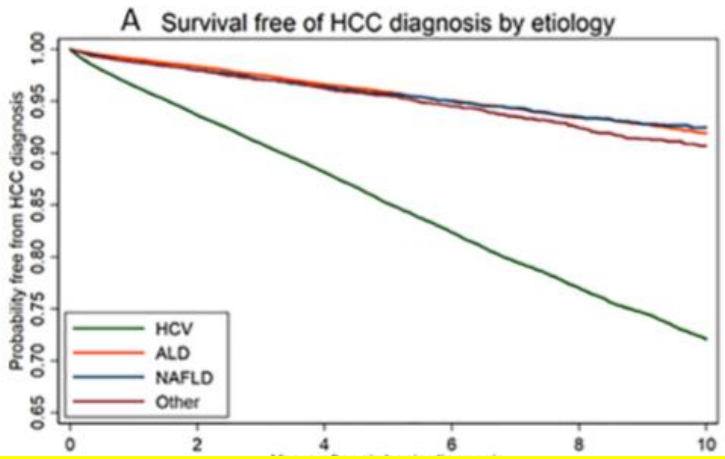
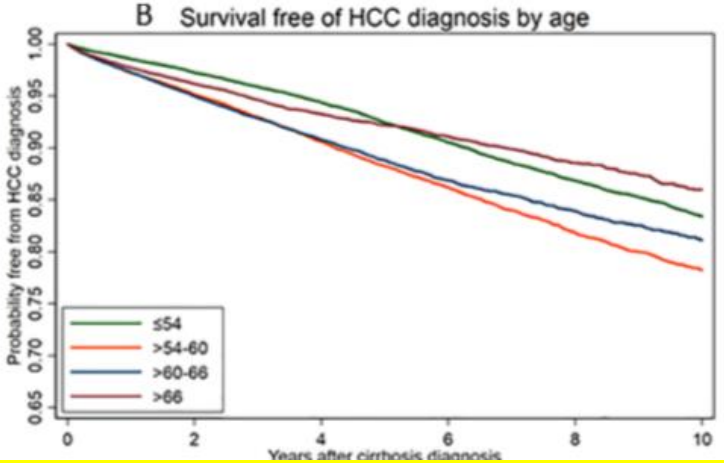
Advances with direct acting antivirals

- Current DAA efficacy and safety means an ability to treat cirrhosis
  - Large numbers of older patients, advanced disease treated with DAA's
- DAAs reduce the mortality that is caused by worsening of liver function
- **HCC**
  - Any increased incidence of HCC would nullify the survival benefits

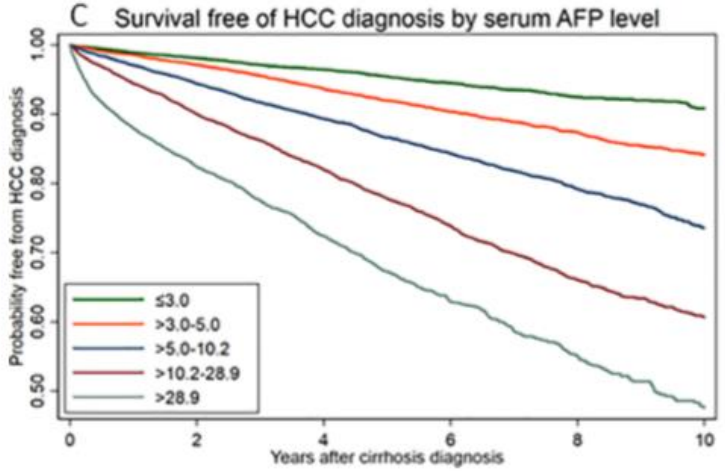
Probability of HCC free by etiology: cirrhosis

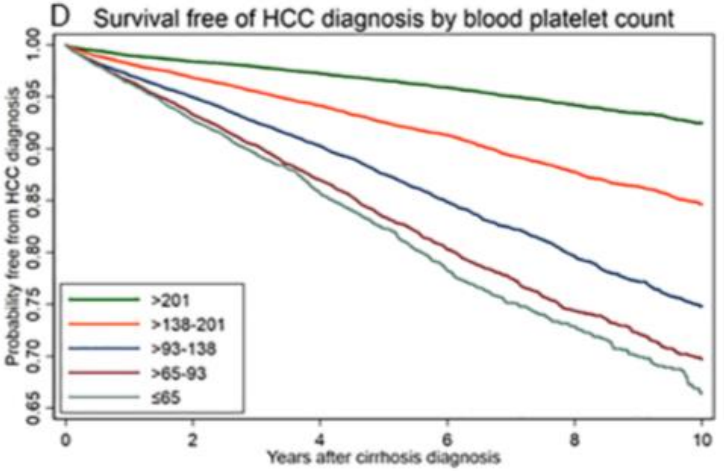
116,404 patients with cirrhosis diagnosed between 2001-2014 VA healthcare and determined incident HCC cases from date of cirrhosis diagnosis until 01/31/2017.





Patients HCV cirrhosis >3 times higher incidence HCC than patients with ALD NAFLD or OTHER (1.0/100

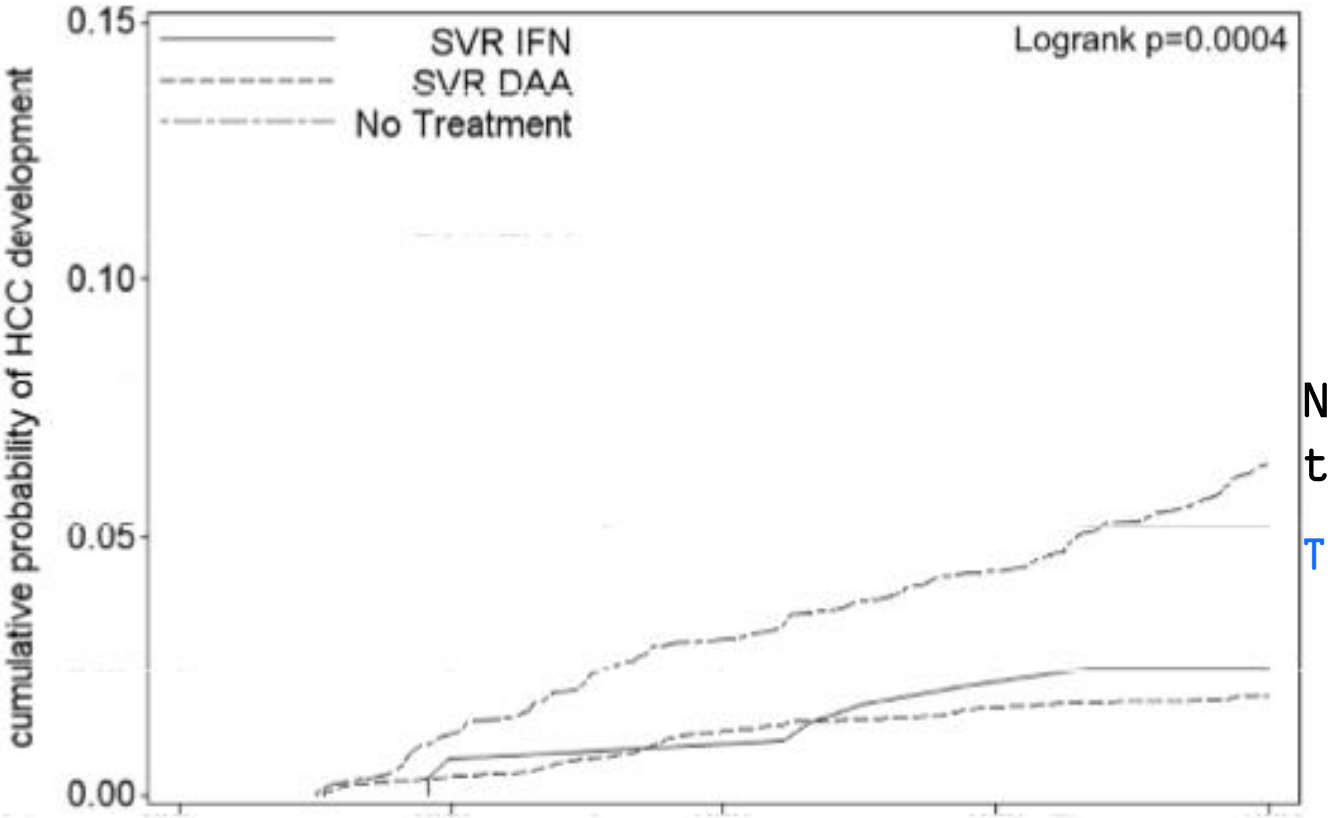




Ioannou, G. N., et al. (2018). PLoS One **13**(9): e0204412.

HCC after SVR with IFN versus DAA: ERCHIVES study

Untreated cirrhosis significantly higher HCC incidence compared to those treated with IFN DAA's: Risk not higher in DAA treated patients



SVR IFN	285	283	280	270	239
SVR DAA	1630	1590	857	297	63
No Treatment	1423	1328	1226	1080	933

No treatment

Treatment S

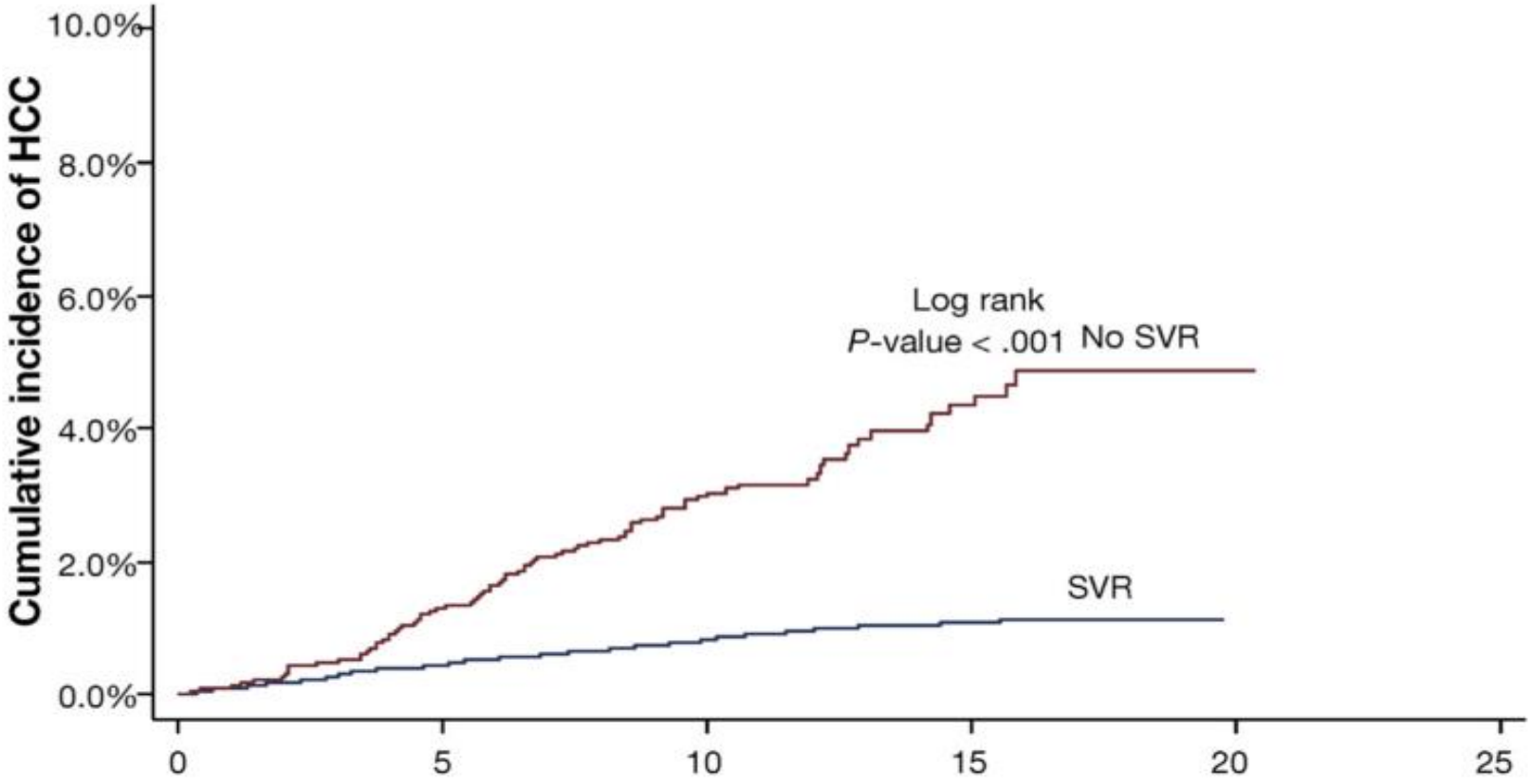
IFN

DAA

Li DK et al. Hepatology (Baltimore, Md). doi: 10.1002/hep.29707 2017.

Cumulative incidence of HCC

ctive cohort study 22,500 patients treated with DAA agen

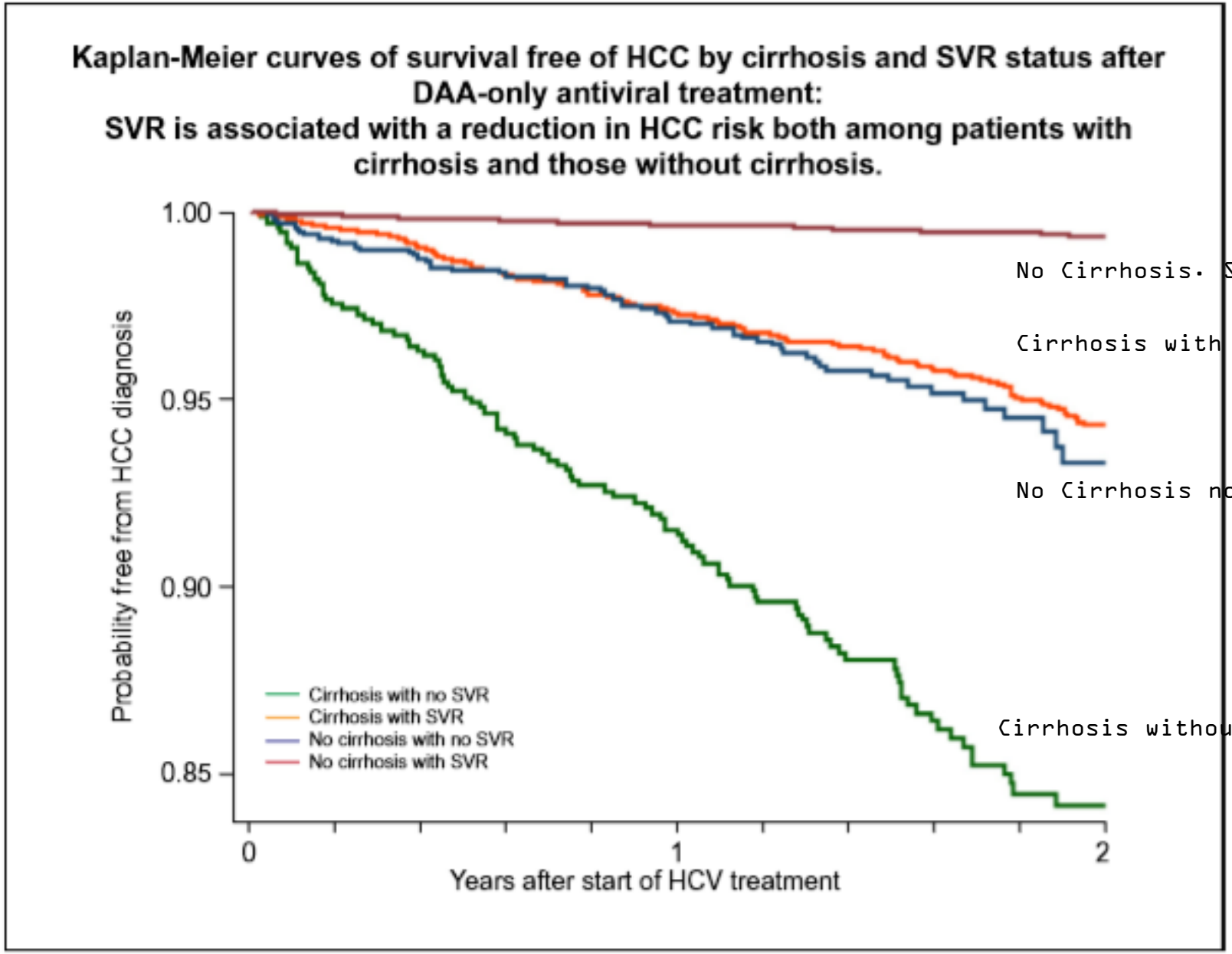


N at risk (N HCC)											
Achieved SVR	19518	(85)	19372	(68)	14364	(29)	6128	(1)	0	(0)	0
No SVR	2982	(35)	2453	(36)	1617	(14)	636	(3)	5	(0)	0

Kanwal F, et al Gastroenterology. 2017;15
Maan and Feld Gastroenterology 2017 153(4

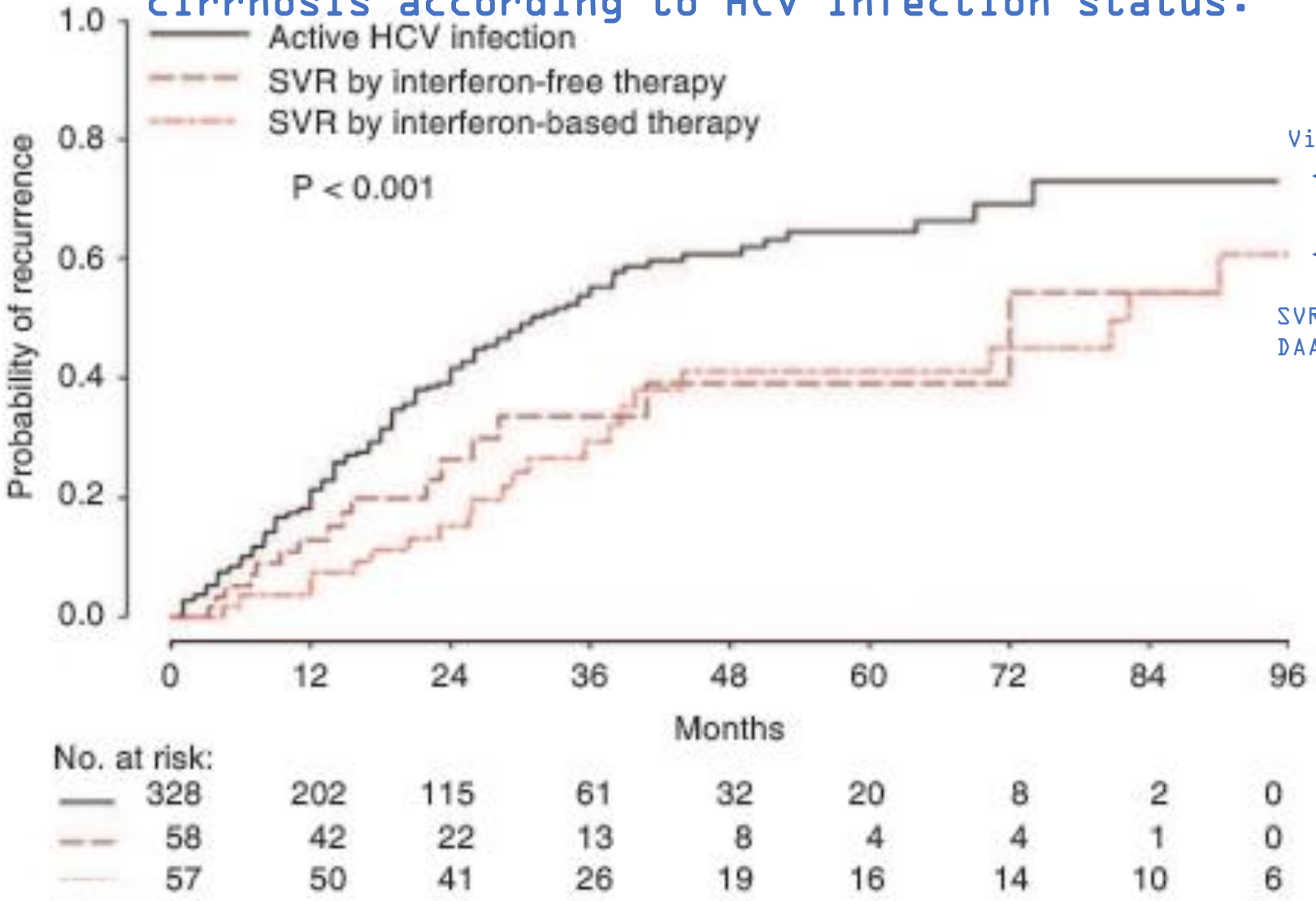
Survival free of HCC by cirrhosis and SVR status after DA

62,354 patients who initiated antiviral treatment VA 1999- 2015 (17 years)



Ioannou GN et al Journal of

Time to HCC recurrence HCC 443 patients with curative resection or ablation of HCC in HCV-related cirrhosis according to HCV infection status:

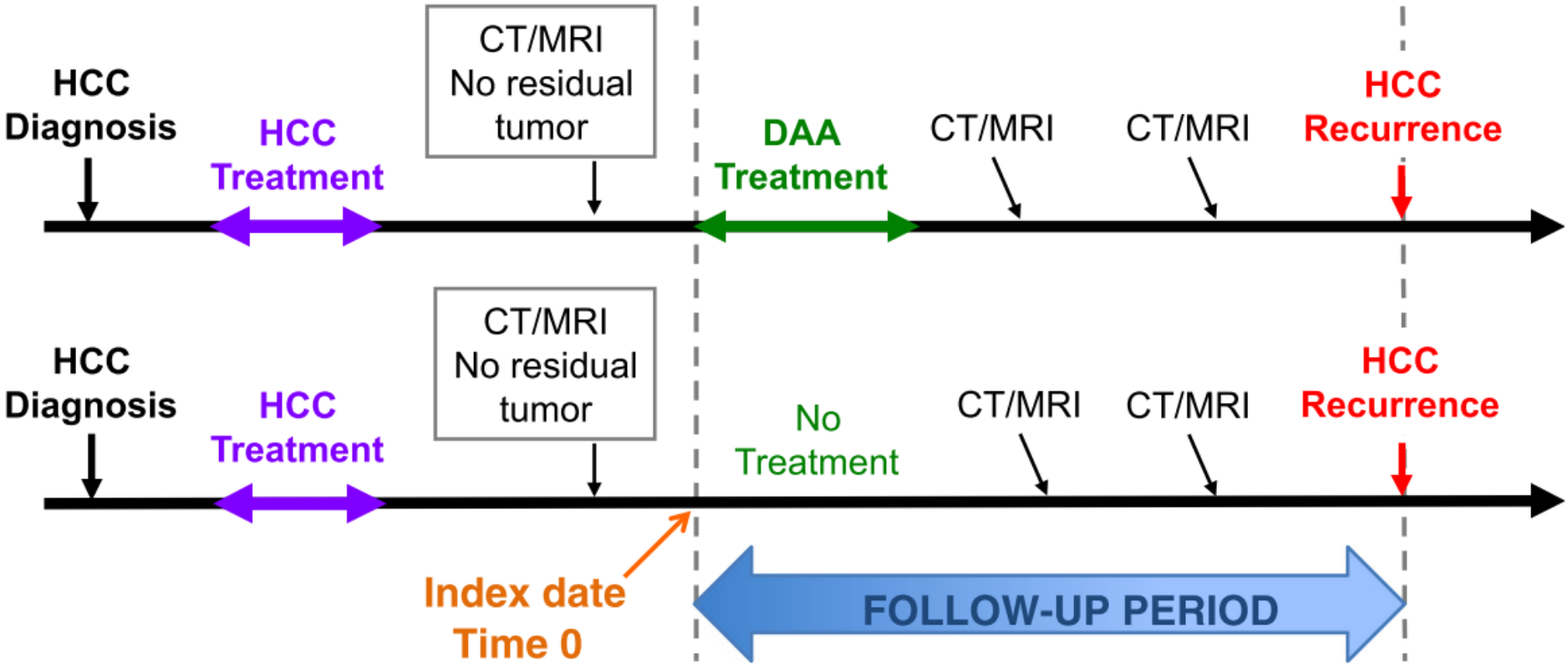


Viremic

SVR by IFN o
DAA

Petta S et al Alimentary pharmacology & therapeuti

Proposed study design for evaluating the risk of recurrent HCC associated with DAA treatment



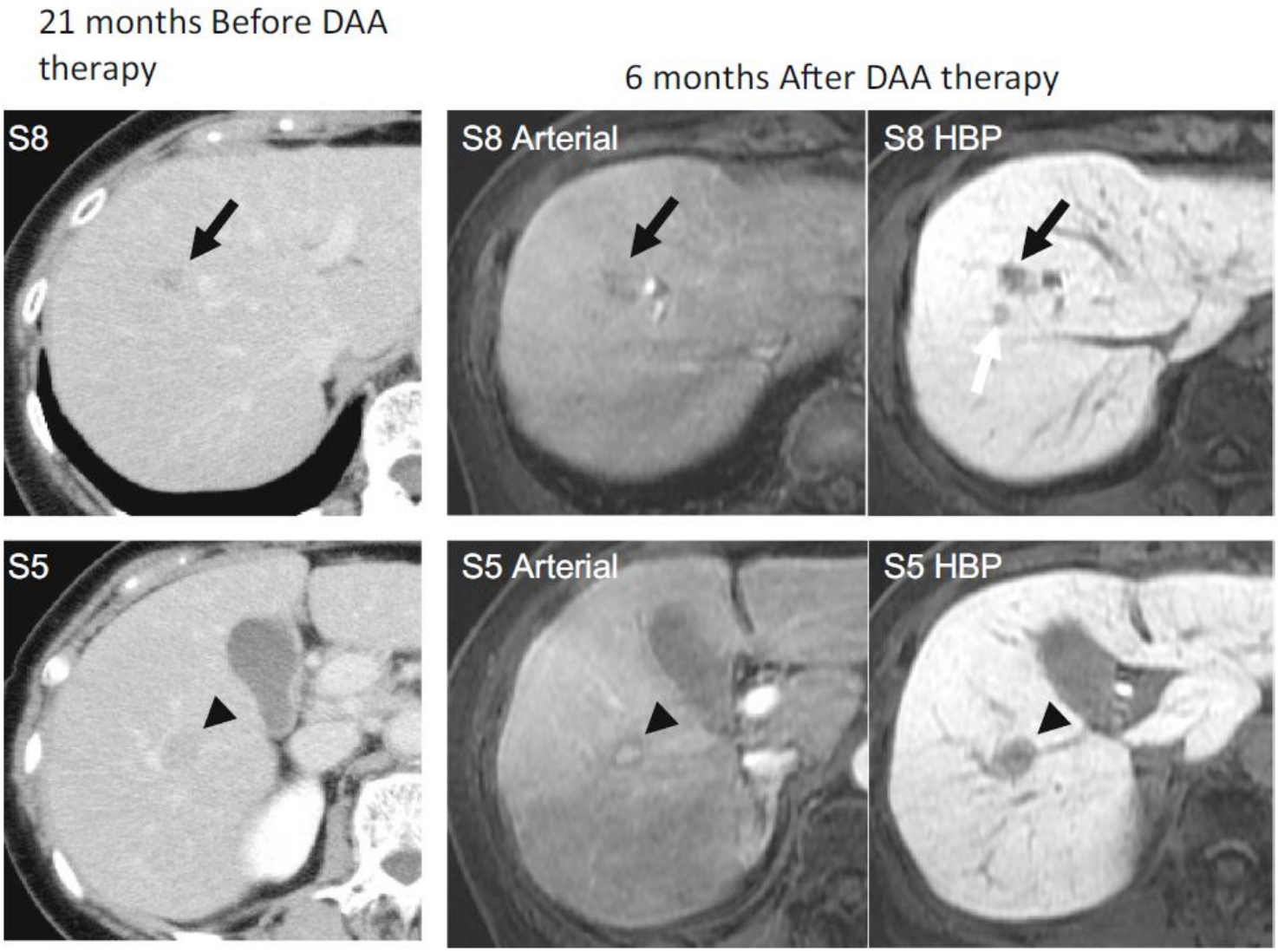
Ioannou, G. N. and J. J. Feld (2019). Gastroenterology **156**(2): 446-460 e442.

Cohort study design required: elements

- Follow-up time begins
  - Start of antiviral therapy treated patients and at the “Index date” for untreated patients
- Evidence of lack of residual tumor
- Date: equal duration time from time of HCC treatment.
- Treated and untreated accounts for immortal time bias: a matching scheme used.
- Comparison between treated and untreated patients adjusted for baseline characteristics that are associated with tumor recurrence
- Treated and untreated patients need to have similar and adequate methods of surveillance for HCC

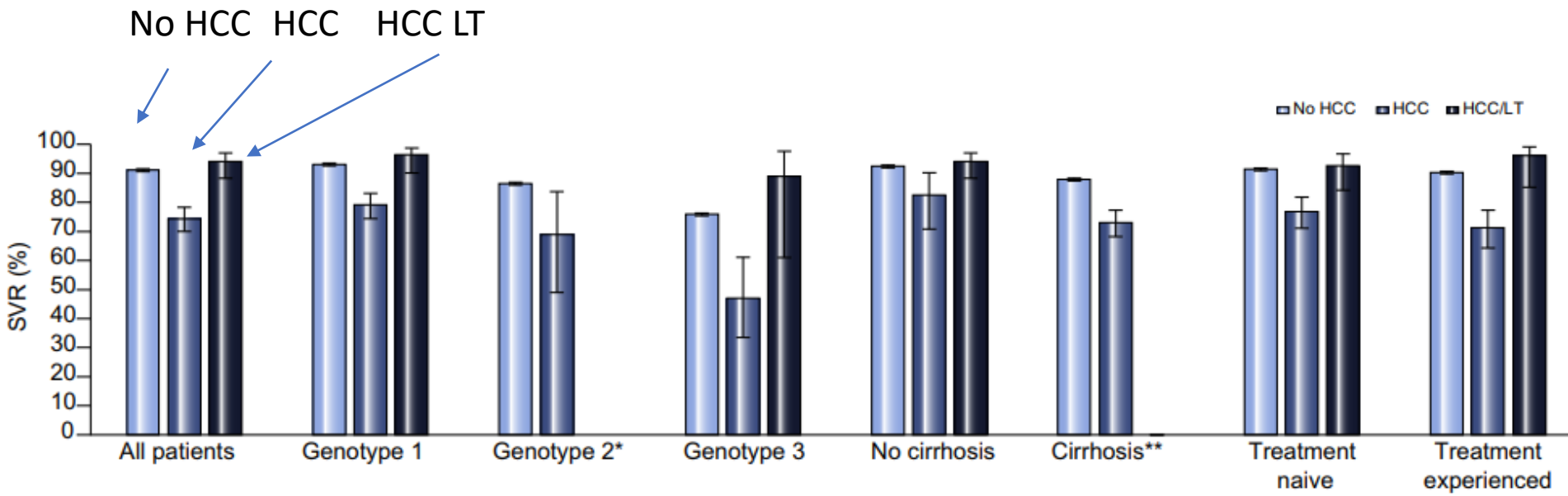
Ioannou, G. N. and J. J. Feld (2019). Gastroenterology **156**(2): 446-460 e442.

Vascularization of hypovascular nodules after DAA therapy.



Ooka, Y., et al. (2018). Hepatol Int **12**(6): 523-530.

SVR rates in patients with HCC, HCC/LT, and no HCC.



Beste, L. A., et al. (2017). J Hepatol **67**(1): 32-39.

Conclusions

- Cohort studies added considerably to knowledge of the natural history and treatment outcome hepatitis C
- Considerable hierarchy of evidence
- Include impact on severe outcomes and resource use – informed policy
- Some cohorts (recurrent HCC DAA) interpretation more difficult
  - Non identical groups, and methodological challenges