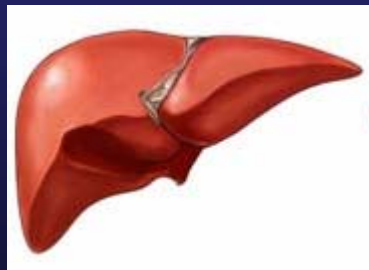


TRATAMIENTO DE LA HEPATITIS C  
EN EL PACIENTE CON CIRROSIS  
BENEFICIO A LARGO PLAZO

Hugo Tanno  
Cátedra de Gastroenterología  
Universidad Nacional de Rosario

# INFECCIÓN HCV



Hígado sano

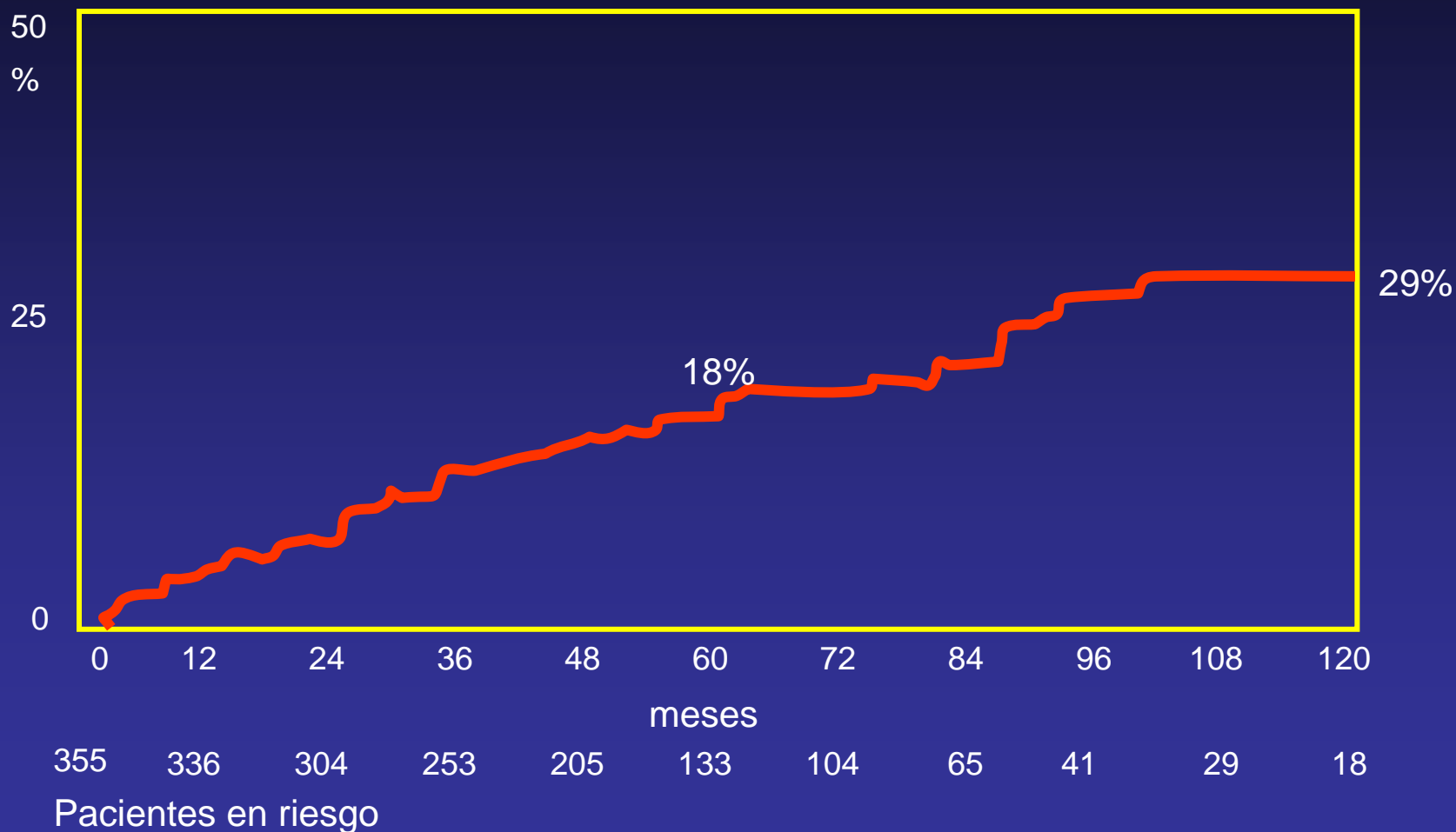


Cirrosis

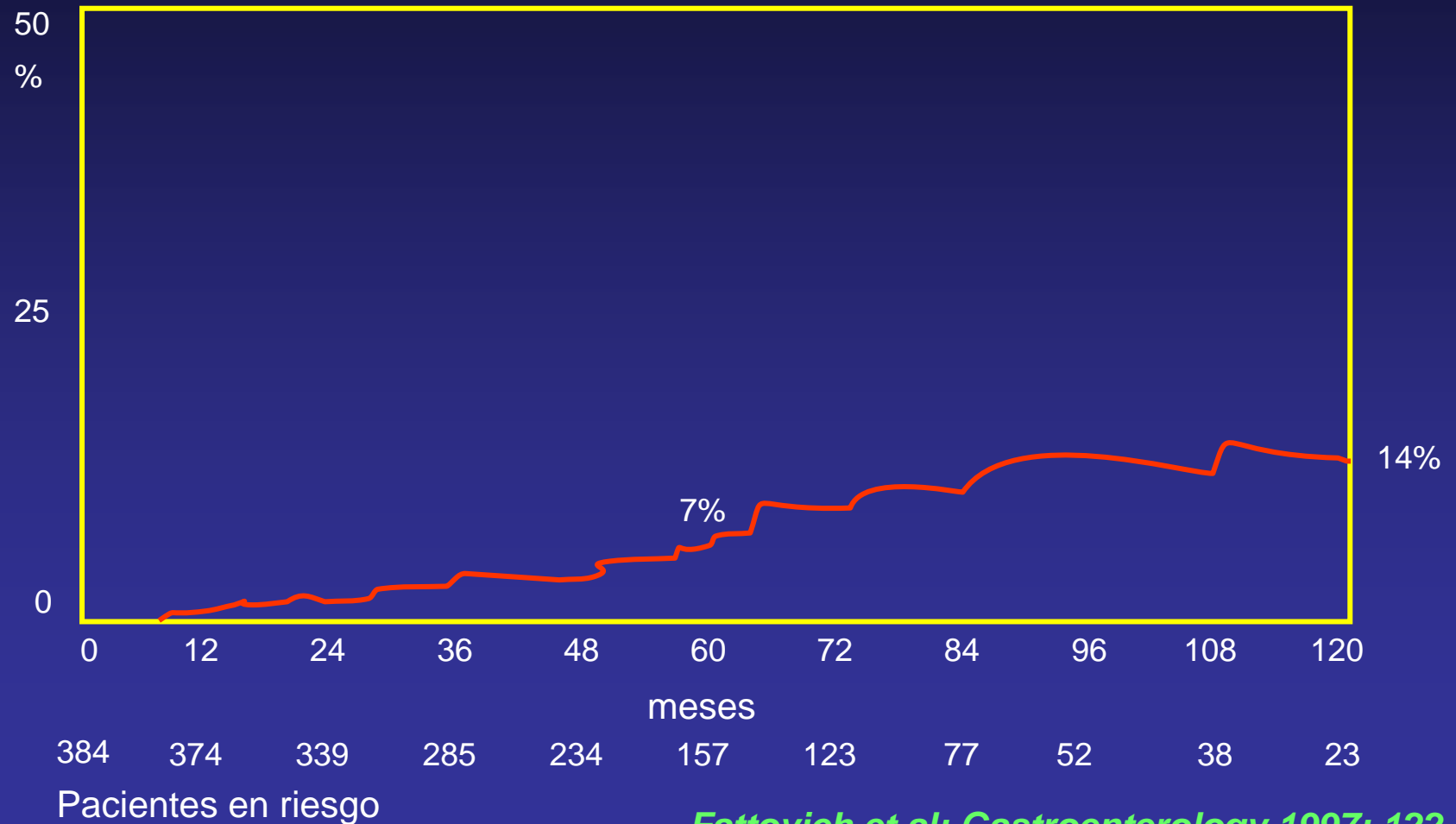


Hepatocarcinoma

# PROBABILIDAD ACUMULADA DE DESARROLLAR UNA DESCOMPENSACIÓN EN PACIENTES CON UNA CIRROSIS COMPENSADA NANB/C QUE NO PRESENTAN HCC

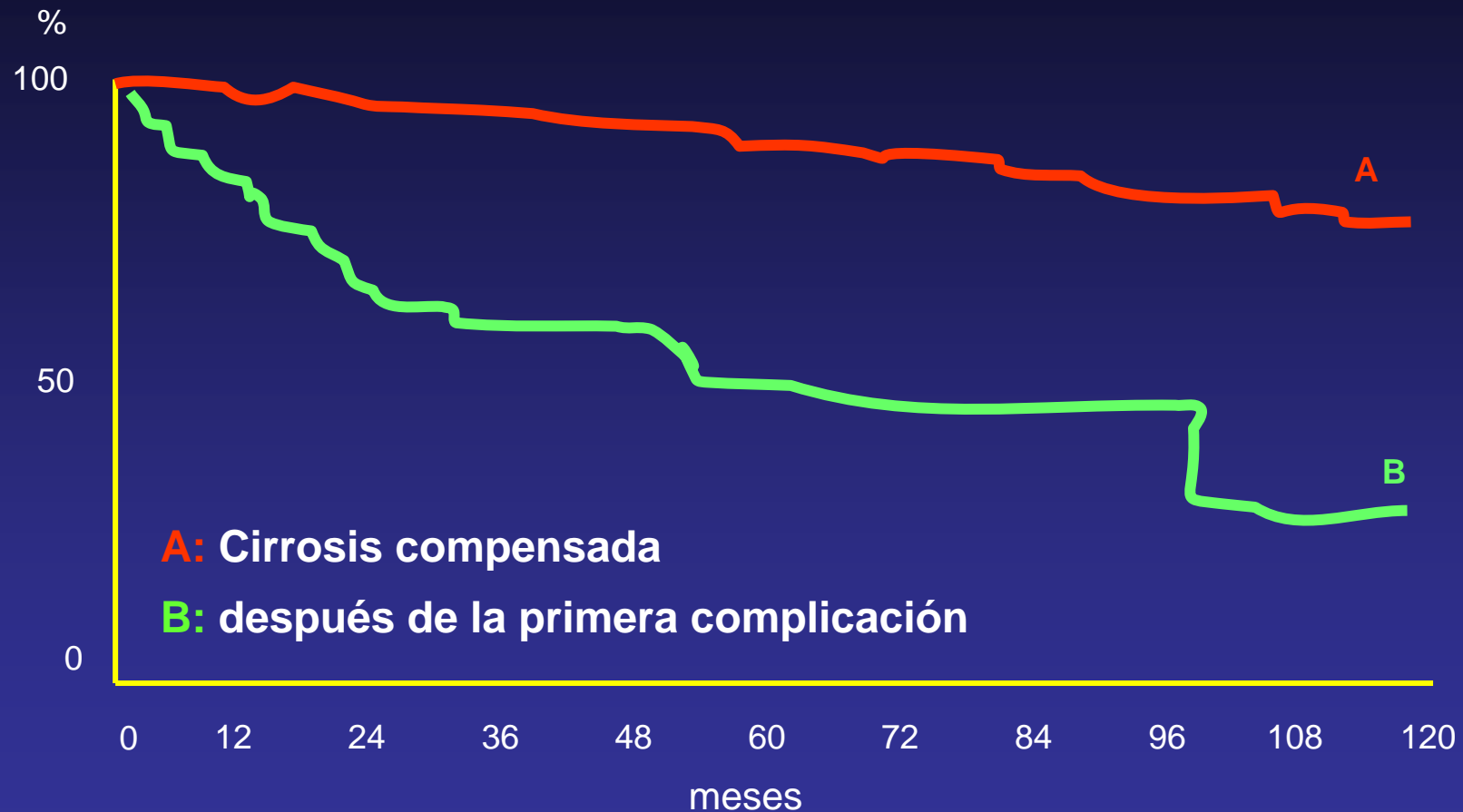


# PROBABILIDAD ACUMULADA DE DESARROLLAR HCC EN PACIENTES CON CIRROSIS COMPENSADA NANB/C



*Fattovich et al; Gastroenterology 1997; 122*

# PROBABILIDAD DE SOBREVIDA DESPUES DEL DIAGNÓSTICO EN PACIENTES CON HEPATITIS NANB/C



**A:** Cirrosis compensada

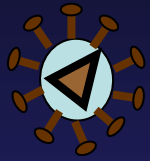
**B:** después de la primera complicación

<b>A</b>	384	376	342	288	236	165	126	79	52	39	25
<b>B</b>	65	39	21	11	7	4	4	3	3	2	1

Pacientes en riesgo

*Fattovich et al; Gastroenterology 1997; 122*

# INFECCIÓN HCV



Tratamiento



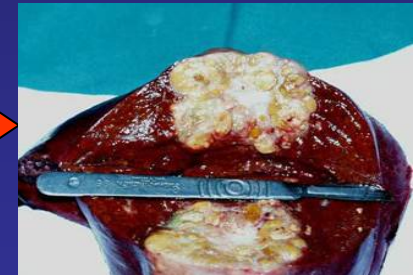
SVR



Hígado sano



Cirrosis



Hepatocarcinoma

# TRATAMIENTO DE LA CIRROSIS HCV

```
graph TD; A[TRATAMIENTO DE LA CIRROSIS HCV] --> B[Child A]; A --> C[Child B - C]; B --> D[Evitar complicaciones  
Prevenir HCC]; C --> E[Evitar infección HCV  
post-transplante];
```

Child A

Evitar complicaciones  
Prevenir HCC

Child B - C

Evitar infección HCV  
post-transplante

# RACIONALIDAD EN EL USO DE IFN EN LA CIRROSIS HCV

Acción antiproliferativa

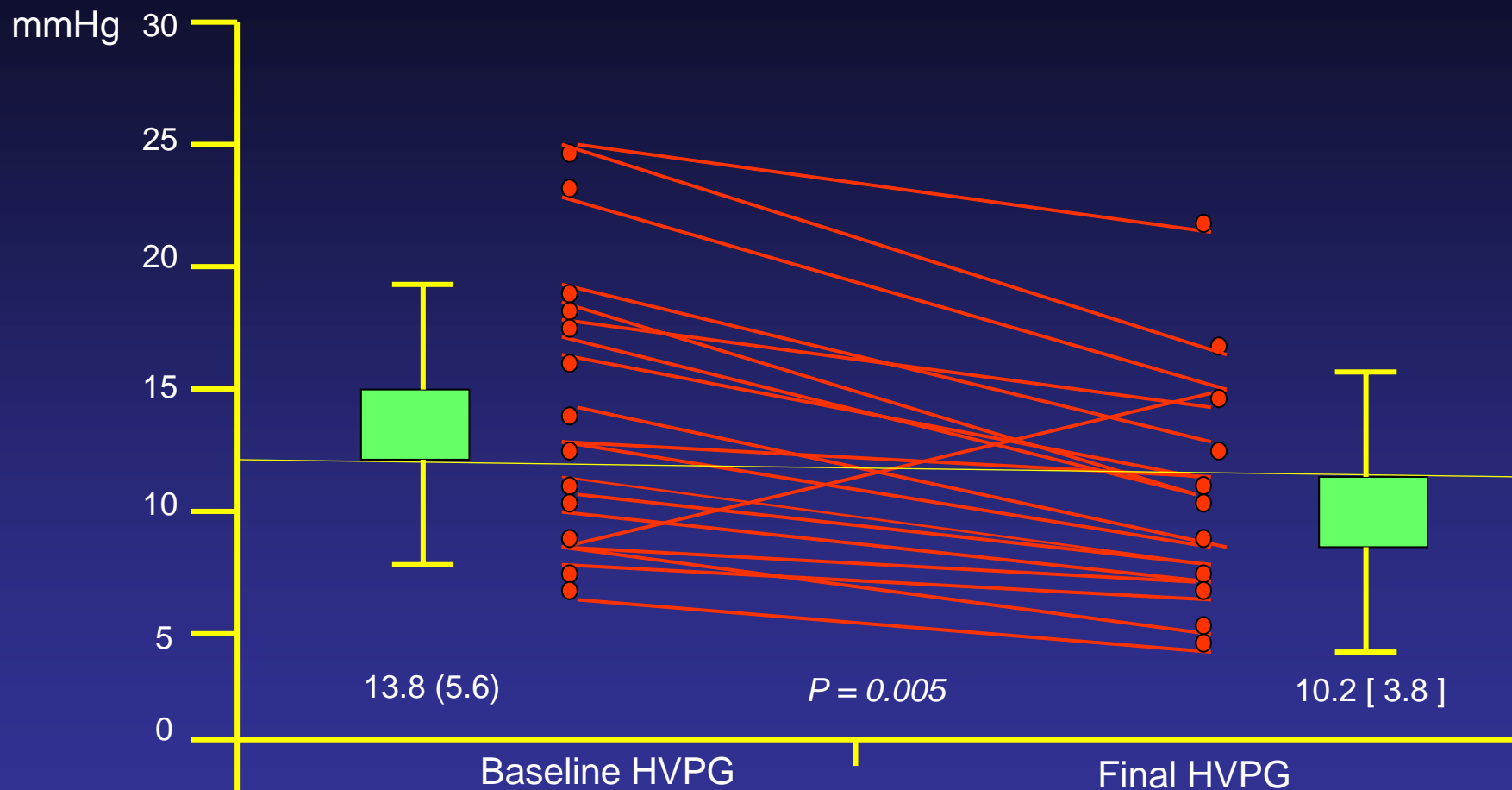
Inhibe la fibrogénesis

Favorece reabsorción de fibrosis

Acción antiviral

Inhibición citoquinas resultantes del daño inmunopatógeno

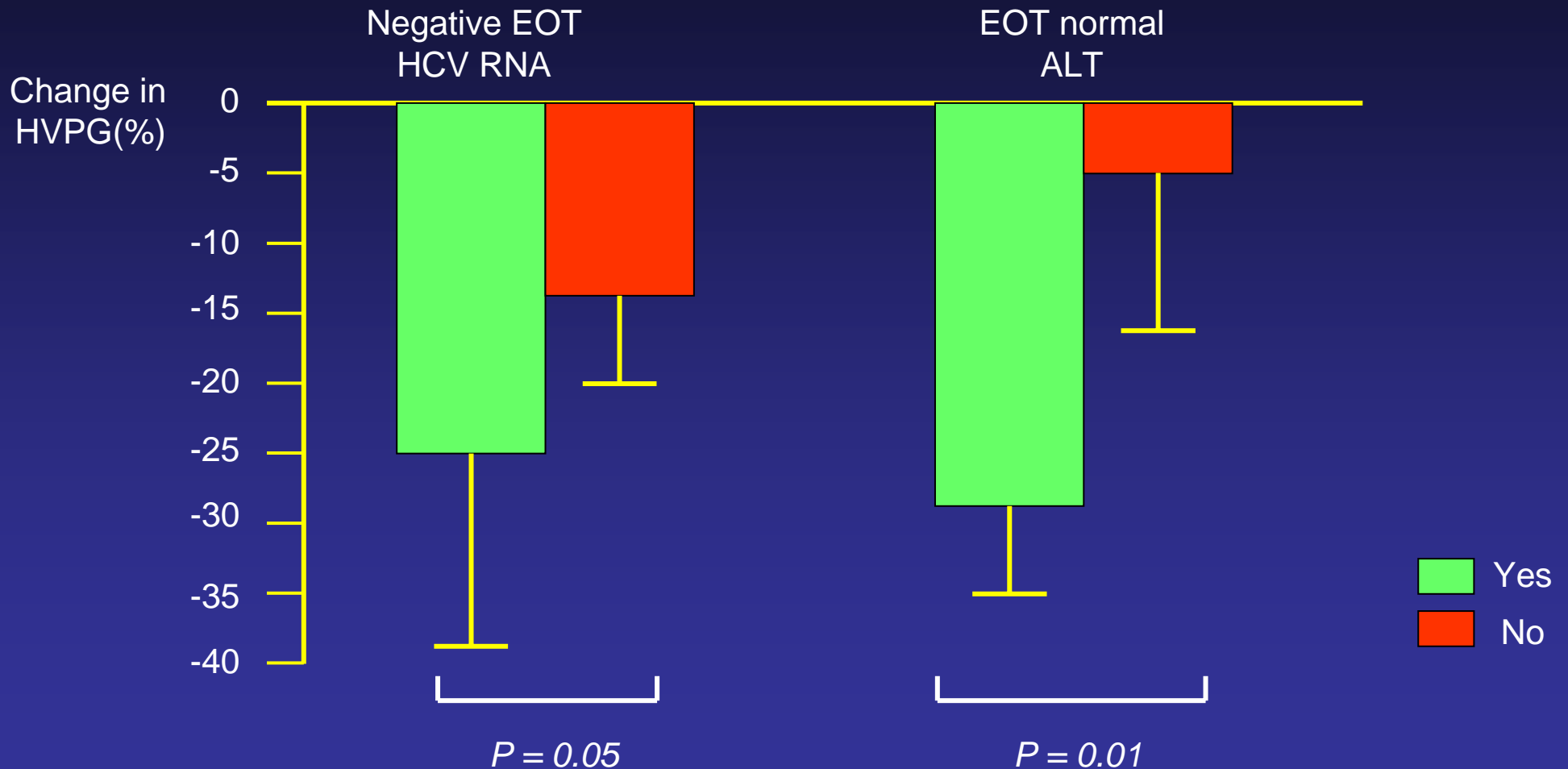
# ANTIVIRAL THERAPY AND HEPATIC VENOUS PRESSURE GRADIENT



Dotted line represents the 12 mmHg threshold

Mean reduction in HVPG: 28.2 (12)%

# EVOLUTION OF HVPG DEPENDING ON EOT VIROLOGICAL RESPONSE AND EOT NORMAL ALT



# TRATAMIENTO DE LA CIRROSIS HCV

Mayor frecuencia  
efectos secundarios



Mayores posibilidades de  
reducción de droga



Menor SVR



- ✓ Mayor edad
- ✓ Trastornos en la microcirculación
- ✓ Dificultad de llegada a la célula infectada
- ✓ Menor tolerancia

# TRATAMIENTO EN PACIENTES CON CIRROSIS HCV

1989 Interferón

2007

1998 IFN + Ribavirina

2000 IFN Peg+Rib.

1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007

Experiencia en años

18 años



# TRATAMIENTO DE LA CIRROSIS HCV

```
graph TD; A[TRATAMIENTO DE LA CIRROSIS HCV] --> B[Child A]; A --> C[Child B - C]; B --> D[Evitar complicaciones  
Prevenir HCC]; C --> E[Evitar infección HCV  
post-transplante];
```

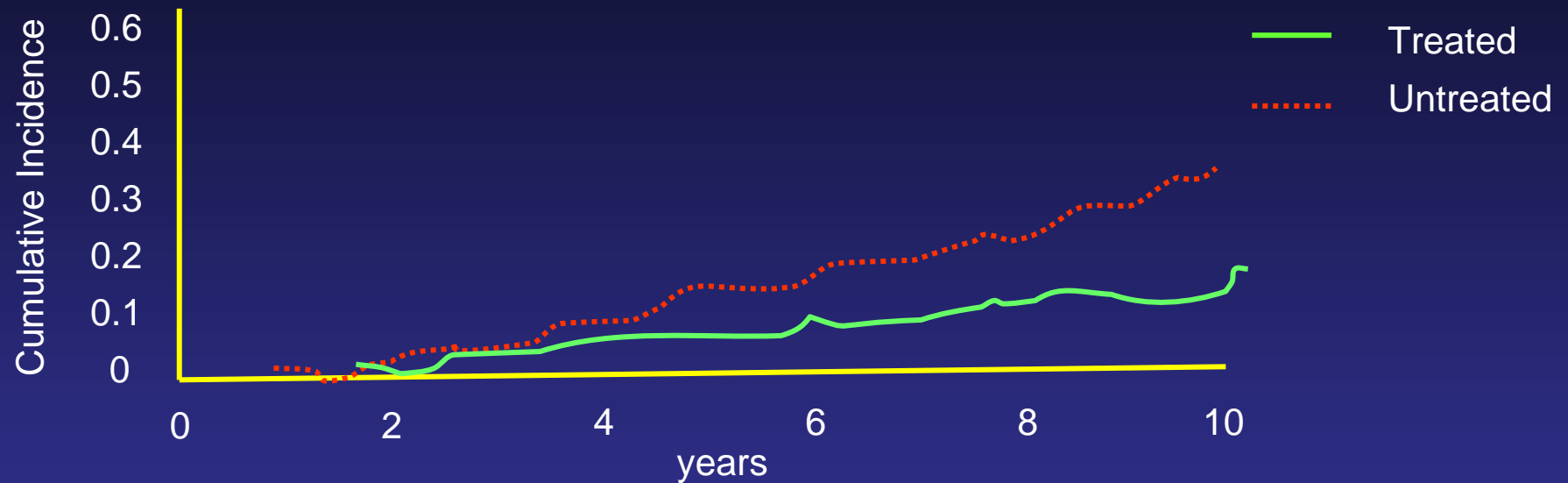
Child A

Evitar complicaciones  
Prevenir HCC

Child B - C

Evitar infección HCV  
post-transplante

# CUMULATIVE INCIDENCE OF HEPATOCELLULAR CARCINOMA AMONG PATIENTS TREATED WITH INTERFERON AND UNTREATED PATIENTS



Untreated patients with HCC	0	17	34	42	54
Patients at risk	490	337	156	114	88

Interferon treated patients with HCC	0	37	73	84	88
Patients at risk	2400	1872	781	200	48

# RELATION OF INTERFERON RESPONSE TO RISK FOR HEPATOCELLULAR CARCINOMA\*

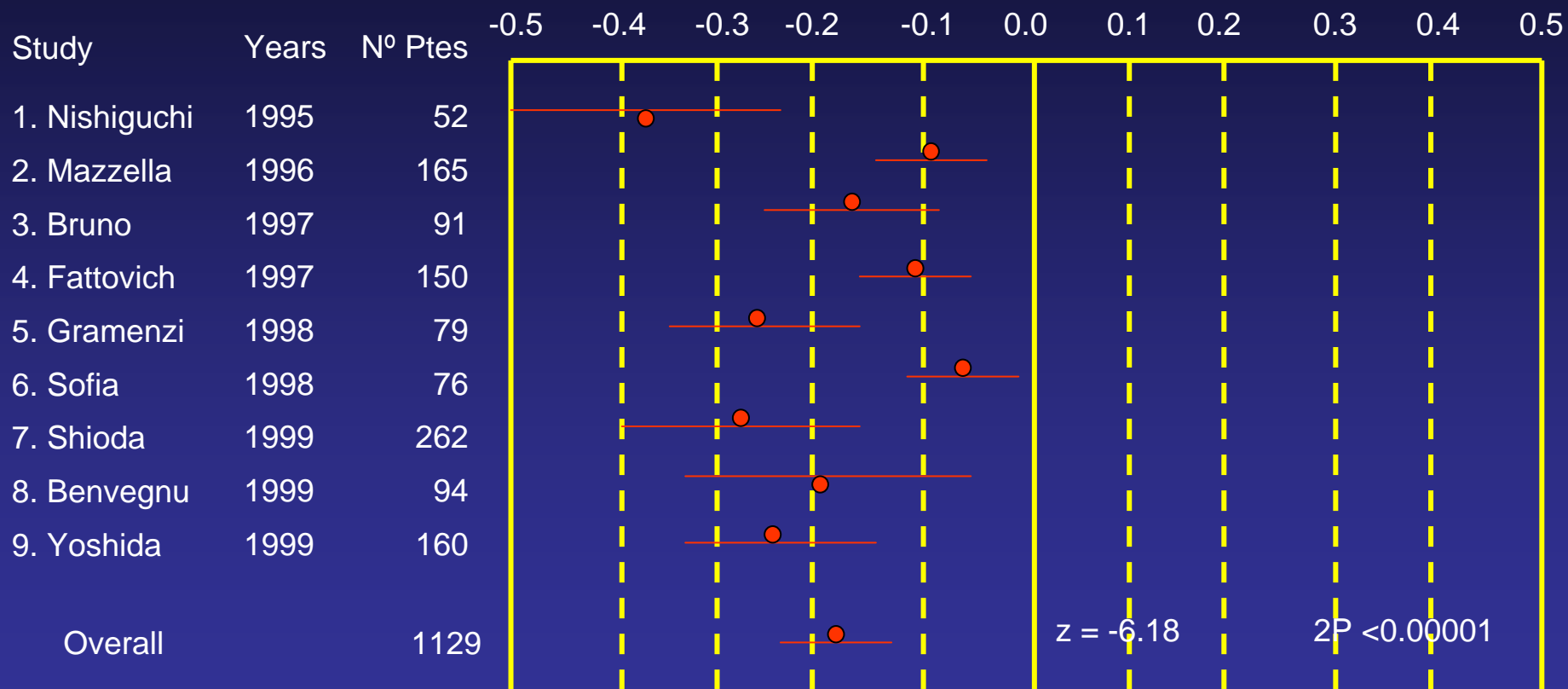
Type of Response	Patients'n	Risk Ratio(95% CI)†	P Value
Virologic response			
Sustained	789	0.197(0.099-0.392)	<0.001
Nonsustained	1568	0.631(0.434-0.918)	0.016
Biochemical response			
Sustained	984	0.197(0.104-0.375)	<0.001
Nonsustained			
Mildly elevated	651	0.358(0.206-0.622)	<0.001
Highly elevated	722	0.910(0.616-1.344)	>0.2
Sustained virologic response			
Sustained	789	0.250(0.131-0.478)	<0.001
Nonsustained with normal ALT level	260	0.271(0.086-0.856)	0.026

\* ALT = alanine aminotransferase

† Risk ratio for hepatocellular carcinoma (145 events among 2847 patients) was calculated by using Cox proportional hazards regression analysis, excluding 43 patients whose response to interferon was not determined. Risk ratios are adjusted for age, sex, and stage of liver fibrosis

# META-ANALYSIS OF THE NINE TRIALS COMPARING SUSTAINED RESPONDERS TO UNTREATED CONTROLS OF IFN FOR PREVENTION OF HCC, IN PATIENTS WITH HCV RELATED CIRRHOSIS

Randon Effects Model (DerSimonian & Laird) Risk Difference 95% CI



Studies arranged by increasing year

Favors Sustained Responders

Favors Controls

# RISK OF DEVELOPMENT OF HEPATOCELLULAR CARCINOMA AFTER THERAPY WITH INTERFERON AMONG PATIENTS WITH AND WITHOUT A SUSTAINED VIROLOGICAL RESPONSE (SVR)

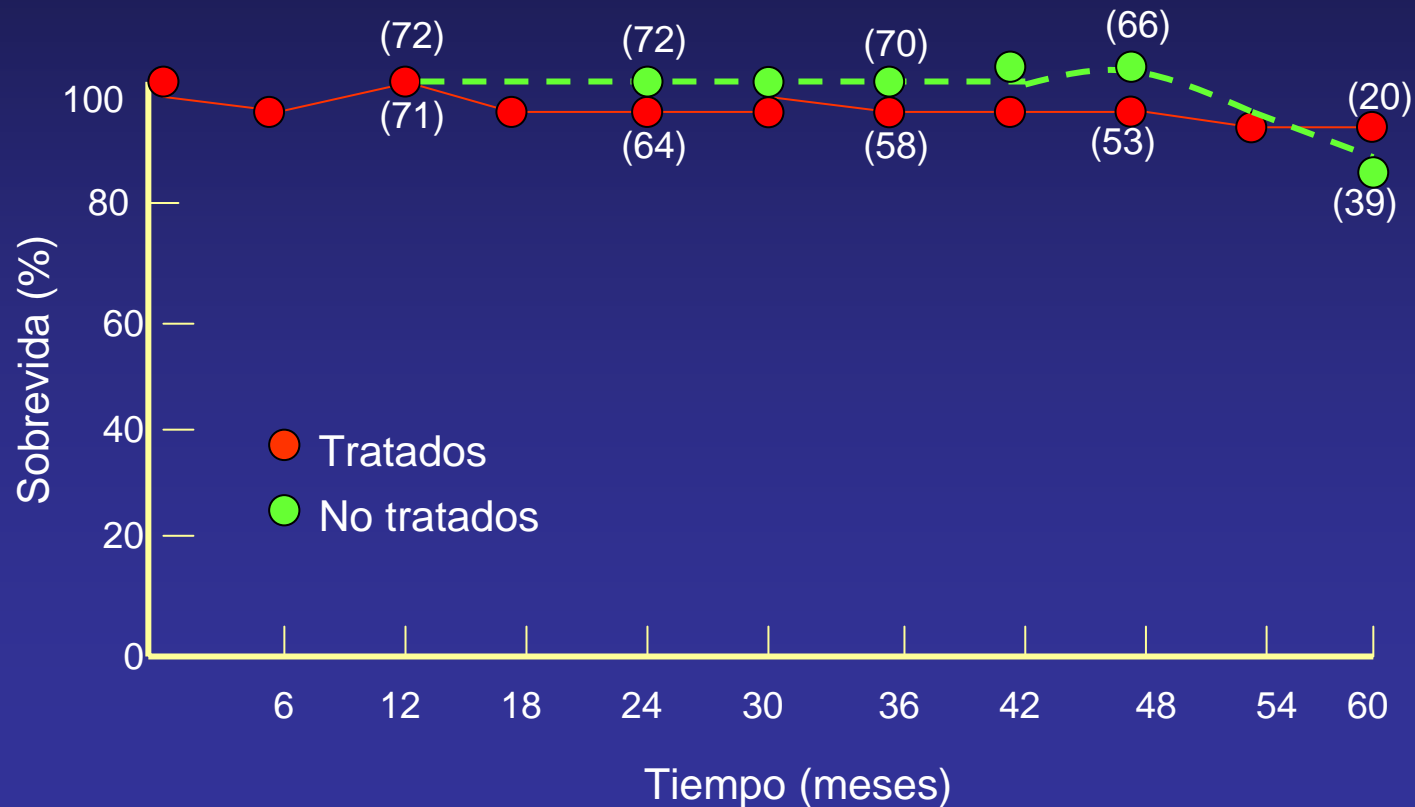
## Relative risk (95% Confidence intervals)

Factor	SVR	Non-SVR
Male vs. Female	1.66 (0.67-4.13)	1.97 (1.48-2.62)
Age (y)		
39	1	1
40-49	1	7.61 (1.81-31.93)
50-59	7.67 (1.69-34.72)	17.84 (4.39-72.49)
60+	13.20 (2.93-59.53)	22.36 (5.48-91.26)
Fibrosis stage		
FO/1	1	1
F2	1.76 (0.47-6.67)	2.86 (1.59-5.13)
F3	3.10 (0.86-11.26)	6.19 (3.50-10.95)
F4	4.78 (1.13-20.18)	12.23 (6.81-21.95)

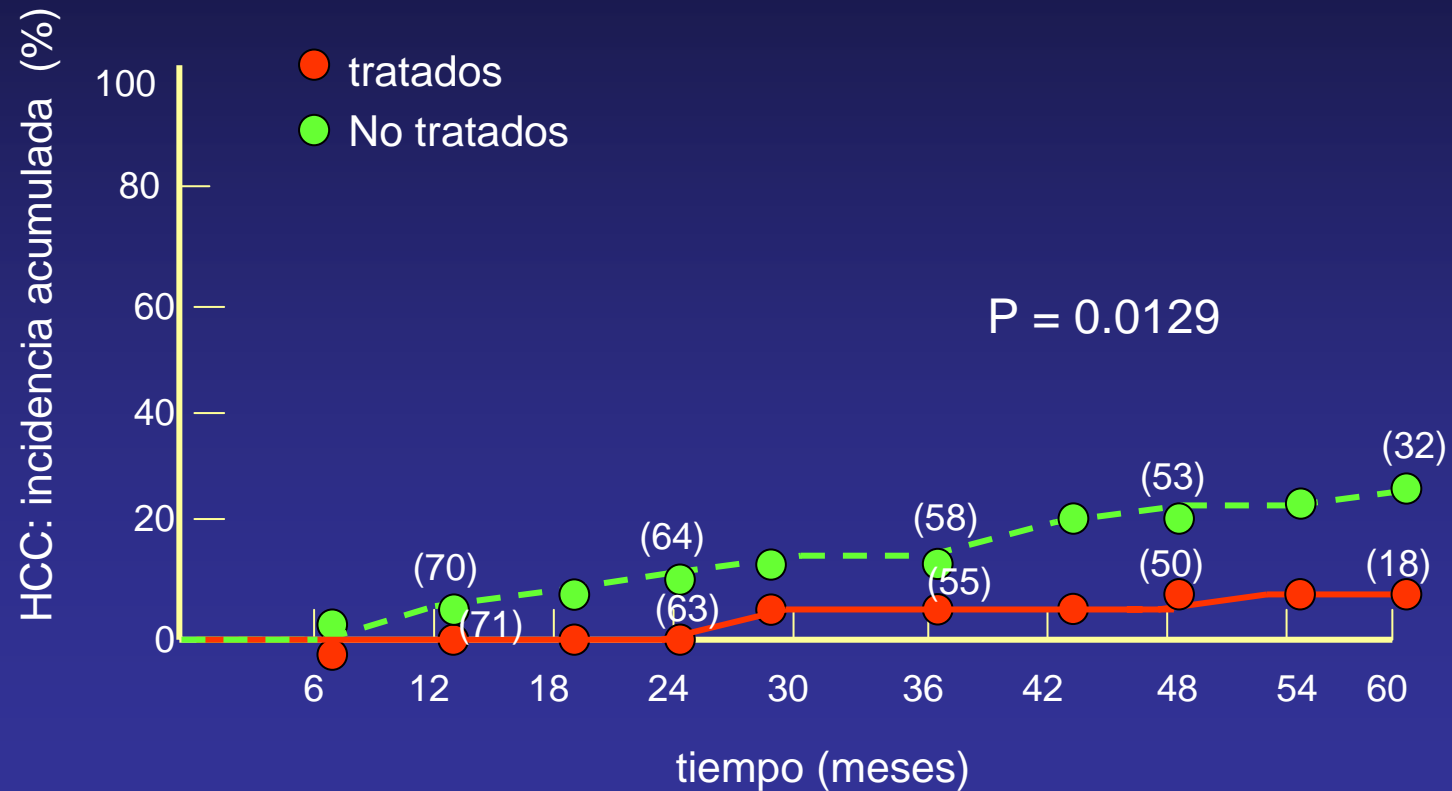
NOTE: Relative Risks were calculated by Cox proportional hazard regression separately in each group.  
Data from Yoshida et al

# IMPACTO DE LA TERAPEUTICA CON INTERFERON EN LA HISTORIA NATURAL DE PACIENTES CON CIRROSIS POR HCV

## PROBABILIDAD ACUMULADA DE SOBREVIDA

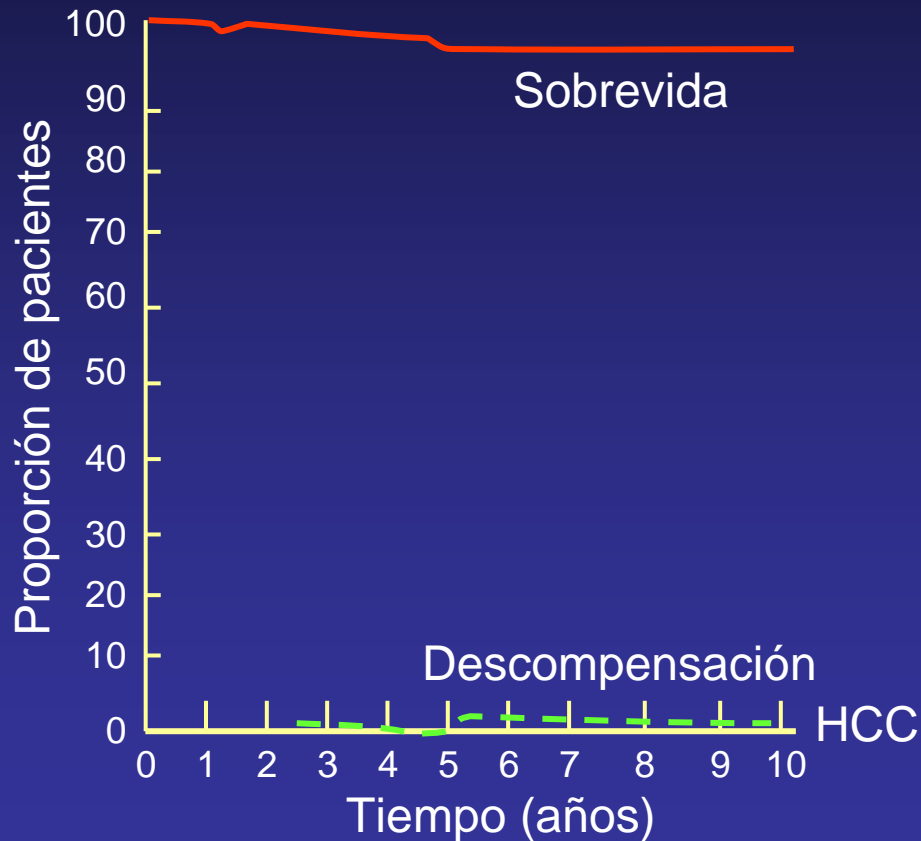


# PROBABILIDAD ACUMULADA DE HCC ENTRE PACIENTES TRATADOS Y NO TRATADOS CON CIRROSIS HCV

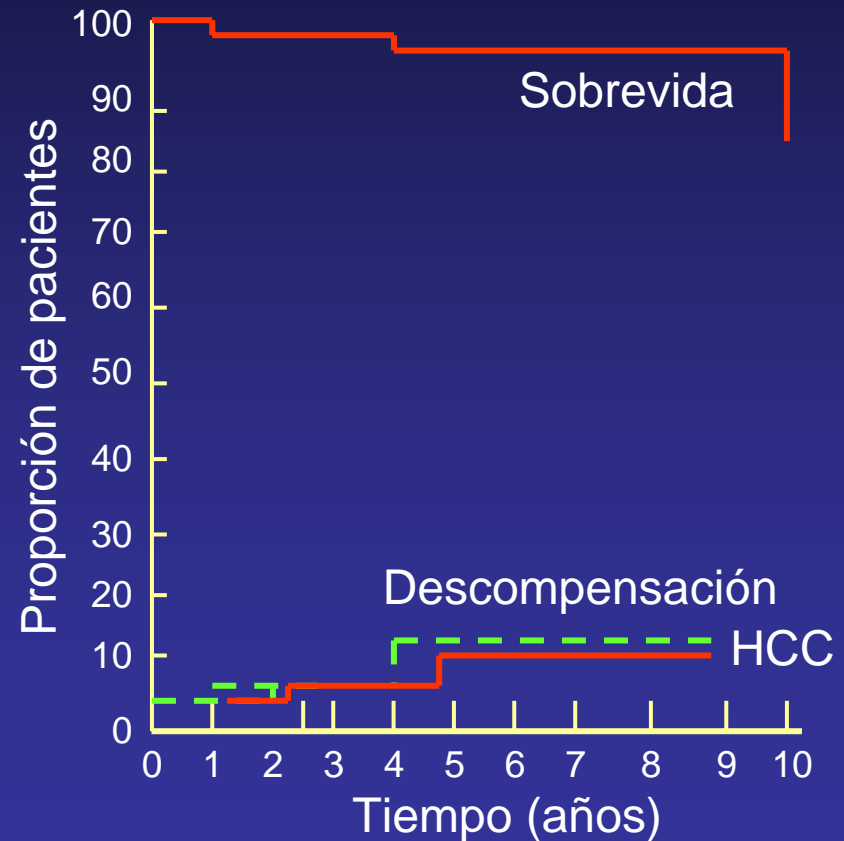


# SOBREVIDA Y DESARROLLO DE EVENTOS CLÍNICOS Y HCC EN PACIENTES CON SVR Y CON RESPUESTA SOSTENIDA

**A Respondedores virológicos sostenidos (SVR) (n = 286)**



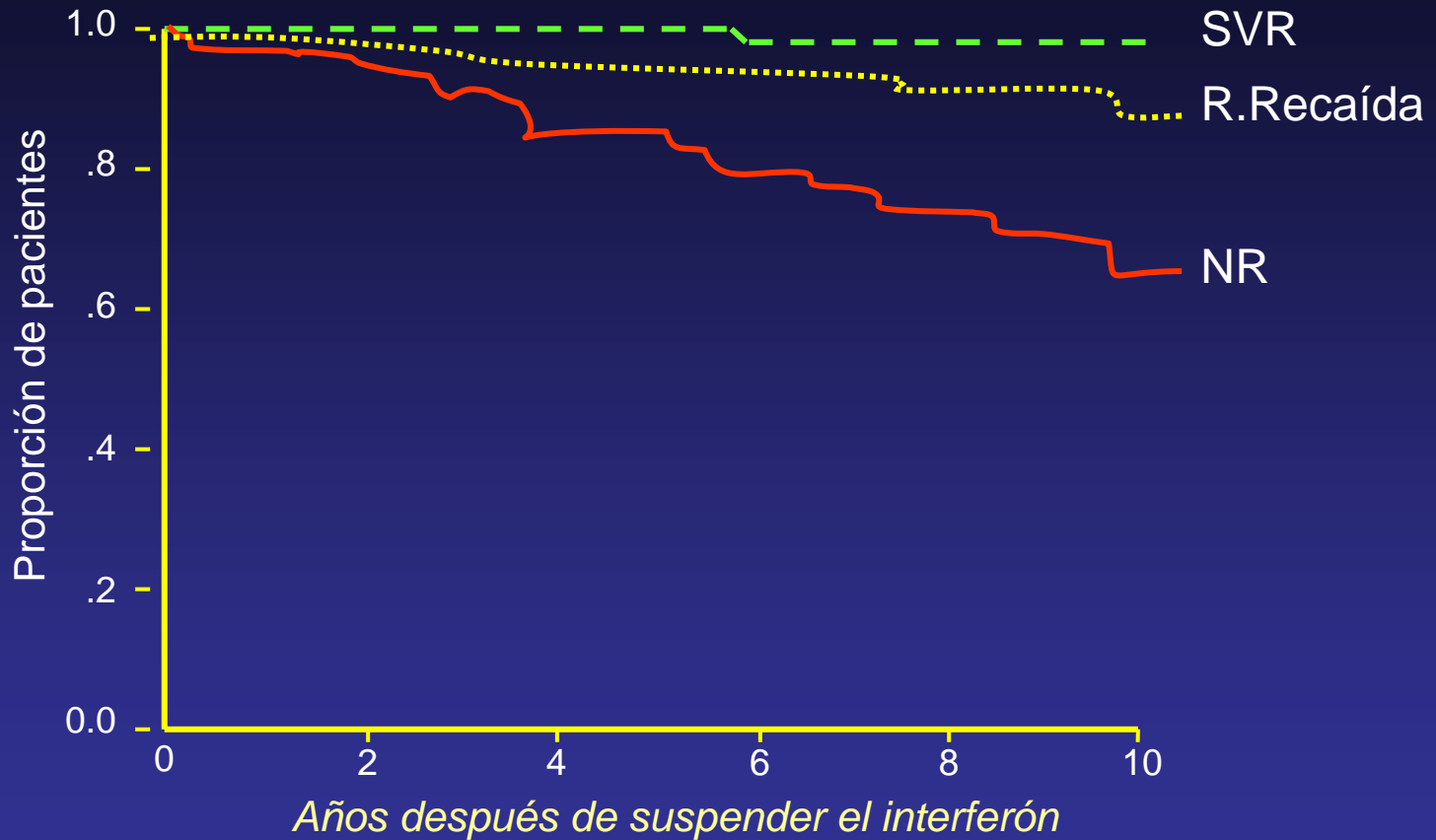
**B Respondedores bioquímicos (n = 50)**



En riesgo: 286 285 270 255 228 171 96 42 15 5 1

En riesgo: 50 48 47 40 37 26 19 9 6 0

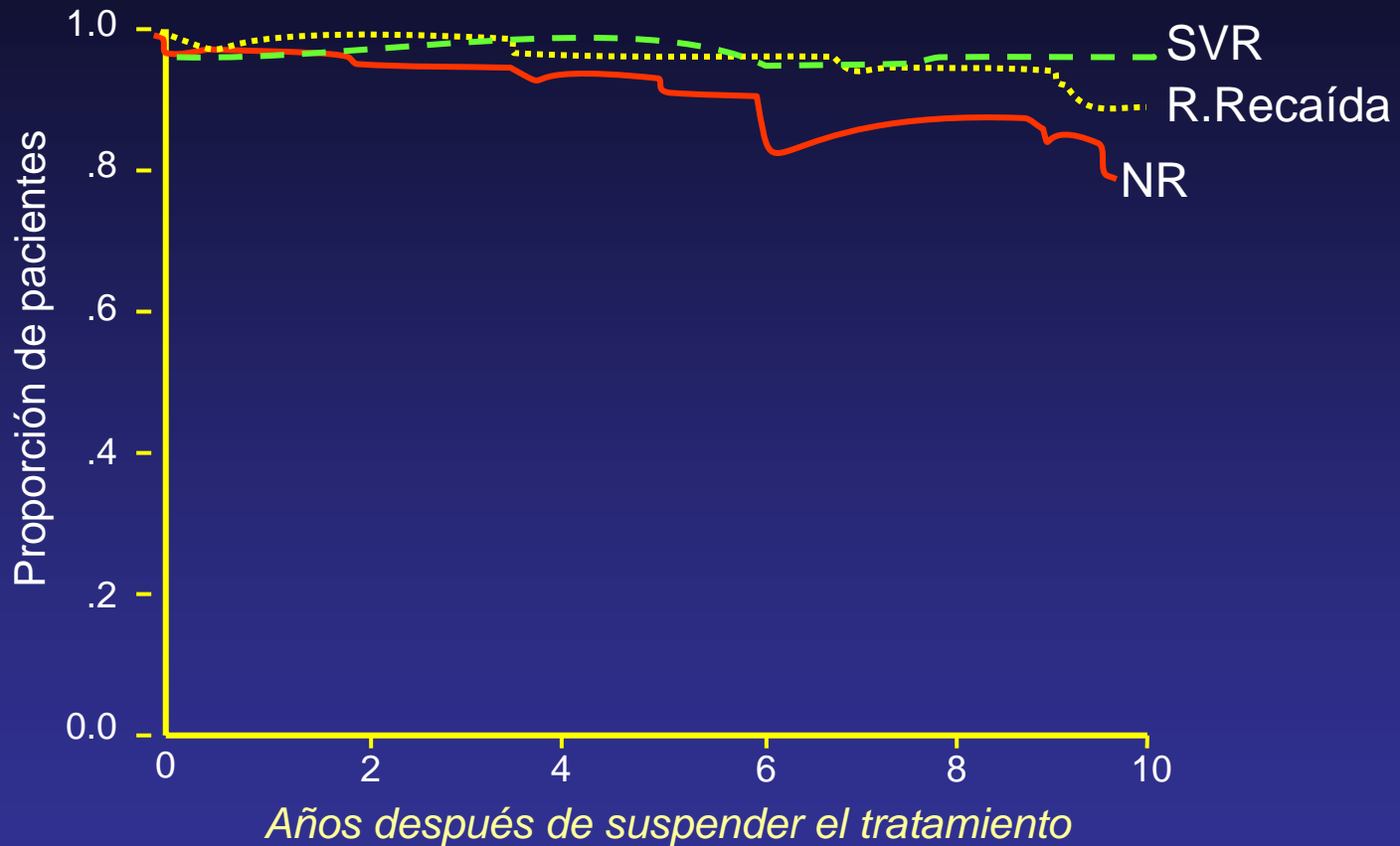
# SOBREVIDA LIBRE DE COMPLICACIONES HEPÁTICAS EN RELACIÓN A LA RESPUESTA AL TRATAMIENTO CON INTERFERÓN



Números de riesgo

50	50	49	42	35	14
136	126	105	93	69	29
157	138	114	36	58	19

# SOBREVIDA SIN HCC EN RELACIÓN A LA RESPUESTA AL TRATAMIENTO CON INTERFERÓN



Números en riesgo

50	50	49	42	35	14
136	127	107	94	70	30
157	141	123	105	68	24

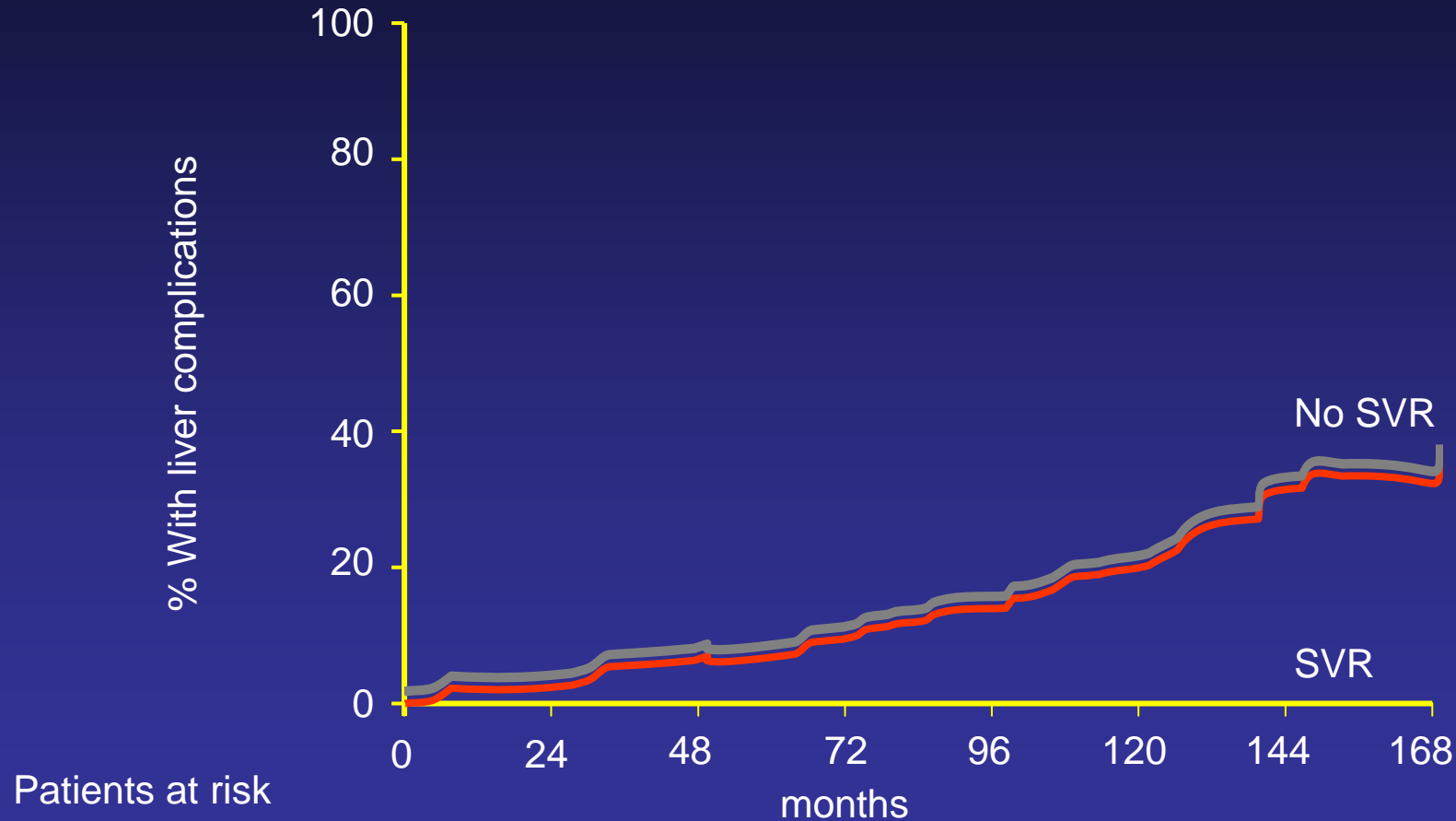
# NUMBER AND RATE OF EVENTS DEVELOPED DURING FOLLOW-UP IN 883 PATIENTS WITH HCV-RELATED HISTOLOGICALLY PROVEN CIRRHOSIS STRATIFIED ACCORDING TO RESPONSE TO IFN

Strata	Person-years	Number of Event	P Value*
Liver-related complications**			
non-SVR	5.703	107	<0.001
SVR	1.061	0	
HCC			
non-SVR	5.805	122	<0.001
SVR	1.055	7	
Liver-related mortality**			
non-SVR	5.781	83	<0.001
SVR	1.019	2	
Non liver-related mortality			
non-SVR	6.004	31	0.2
SVR	1.077	4	

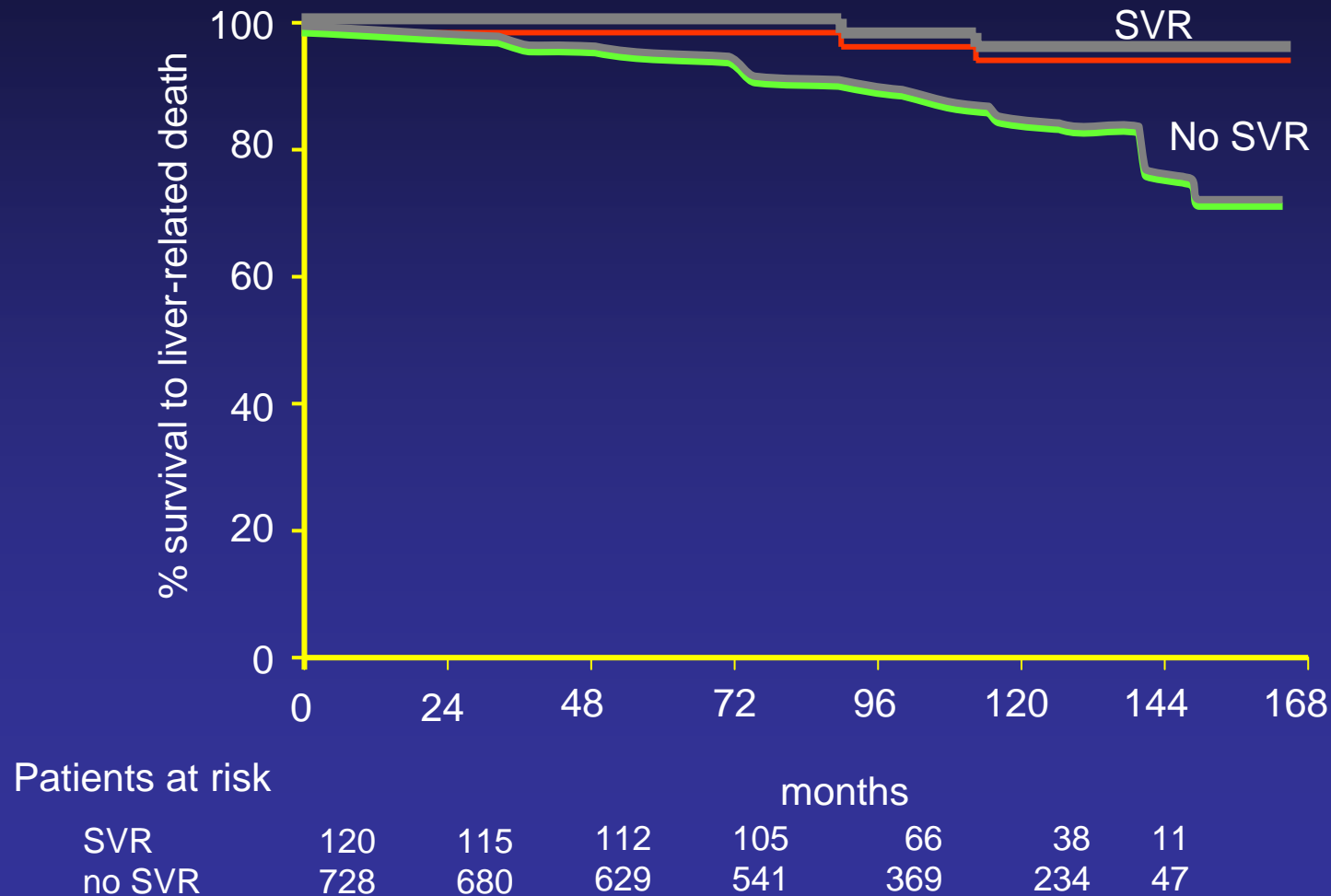
Abbreviations: SVR, sustained virological response; n.a., not applicable

\* By log-rank test \*\*Patients who died of non liver-related causes were excluded

# CUMULATIVE INCIDENCE OF LIVER-RELATED COMPLICATIONS IN 883 PATIENTS WITH HCV-RELATED HISTOLOGICALLY PROVEN CIRRHOSIS STRATIFIED TO RESPONSE TO IFN

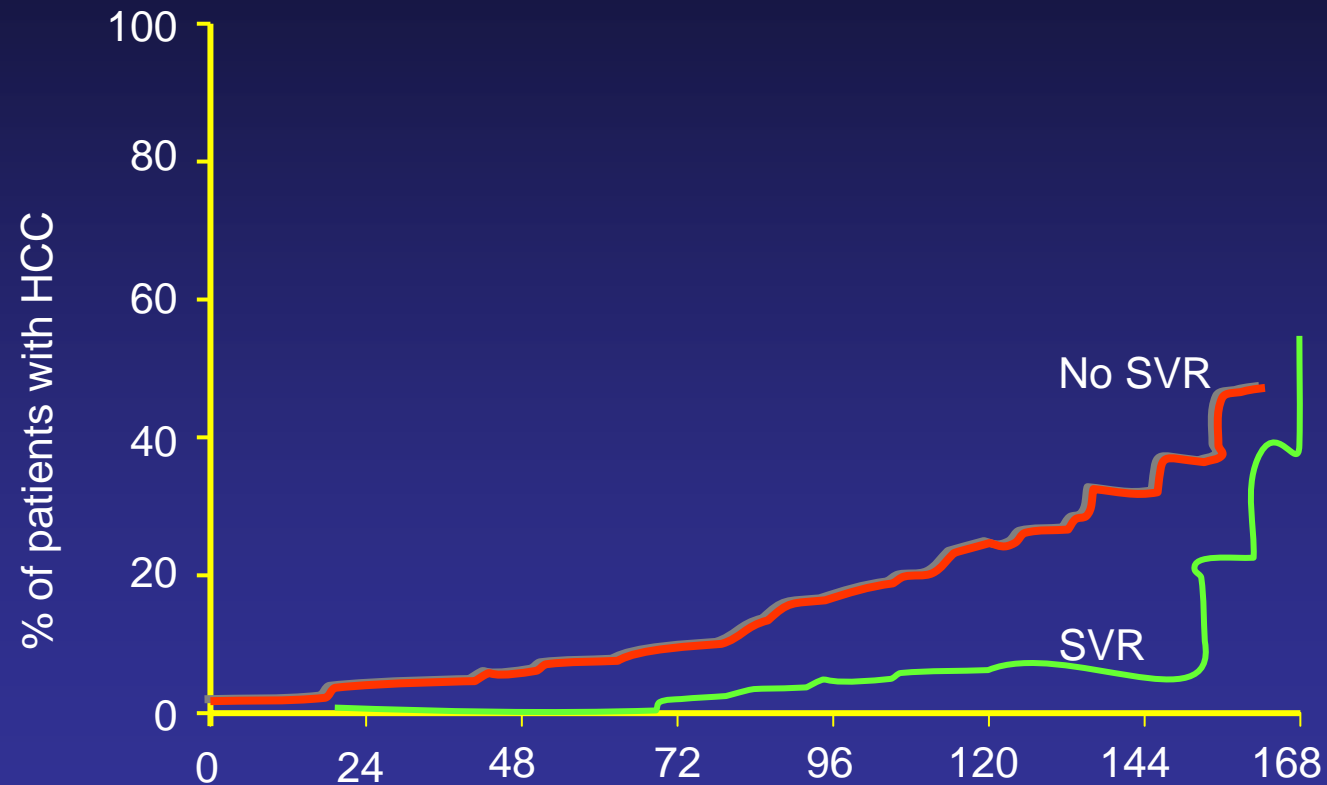


# CUMULATIVE INCIDENCE OF LIVER-RELATED MORTALITY IN 848 PATIENTS WITH HCV-RELATED HISTOLOGICALLY-PROVEN CIRRHOSIS STRATIFIED ACCORDING TO RESPONSE TO IFN



*Bruno et al. Hepatology 2007*

# CUMULATIVE INCIDENCE OF HCC IN 883 PATIENTS WITH HCV-RELATED HISTOLOGICALLY PROVEN CIRRHOSIS STRATIFIED TO RESPONSE TO IFN



Patients at risk

	0	24	48	72	96	120	144	168
SVR	124	119	115	108	69	40	11	
no SVR	759	699	640	541	359	221	41	

months

TRATAMIENTO DE  
PACIENTES HCV CON  
CIRROSIS  
DESCOMPENSADA

# TRATAMIENTO DE LA CIRROSIS HCV

```
graph TD; A[TRATAMIENTO DE LA CIRROSIS HCV] --> B[Child A]; A --> C[Child B - C]; B --> D[Evitar complicaciones  
Prevenir HCC]; C --> E[Evitar infección HCV  
post-transplante];
```

Child A

Evitar complicaciones  
Prevenir HCC

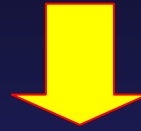
Child B - C

Evitar infección HCV  
post-transplante

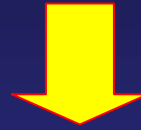
# HISTORIA NATURAL DE LA HEPATITIS C

## Post-Tx

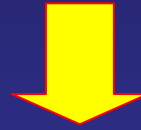
**Recurrencia de la infección por HCV**



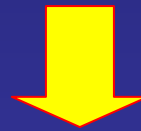
**Hepatitis en el injerto del 80-100% de los pacientes**



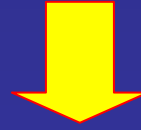
**Rápida Fibrogénesis**



**Evolución acelerada a cirrosis**

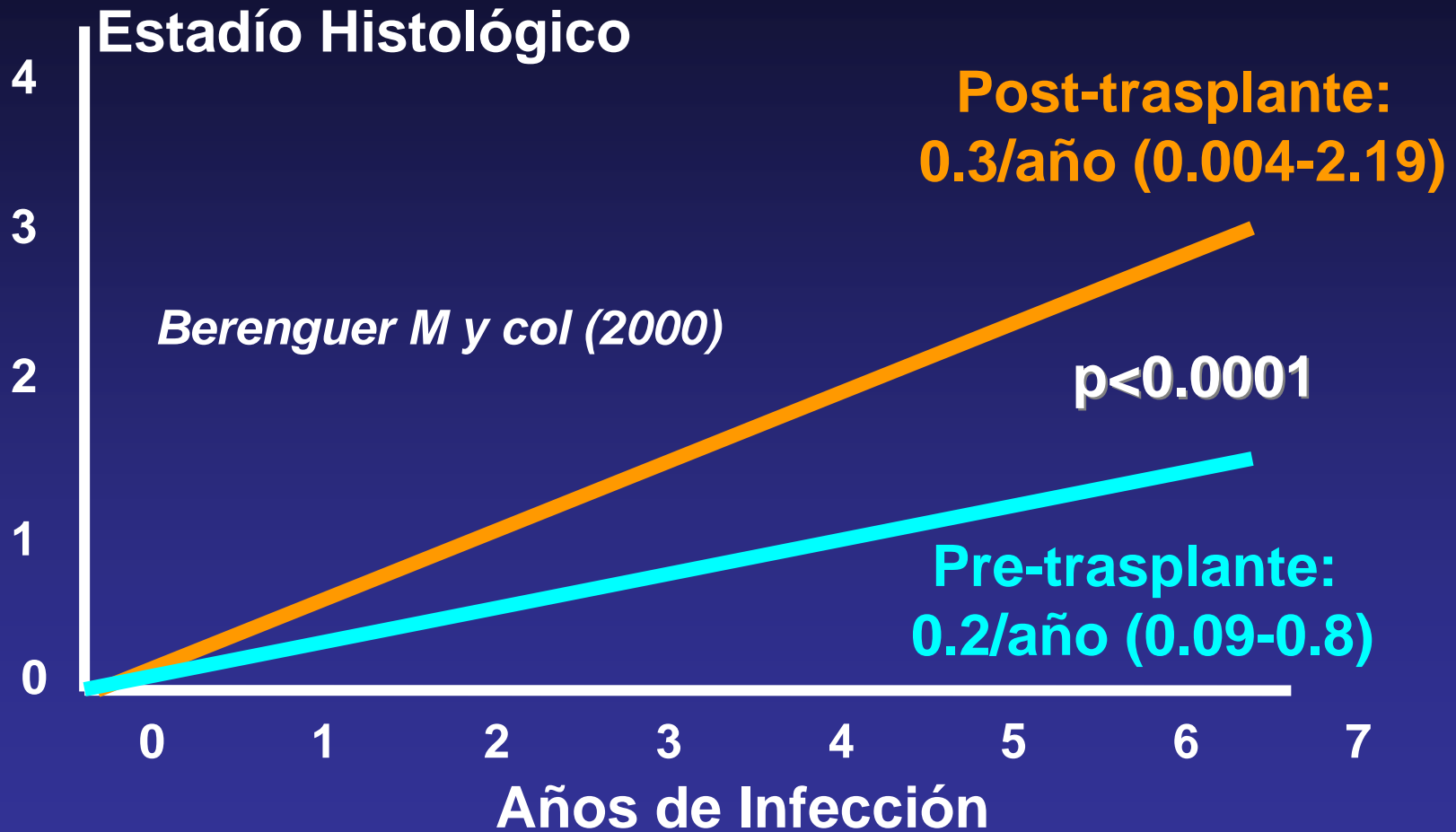


**Disminución de la sobrevida (injerto y paciente)**



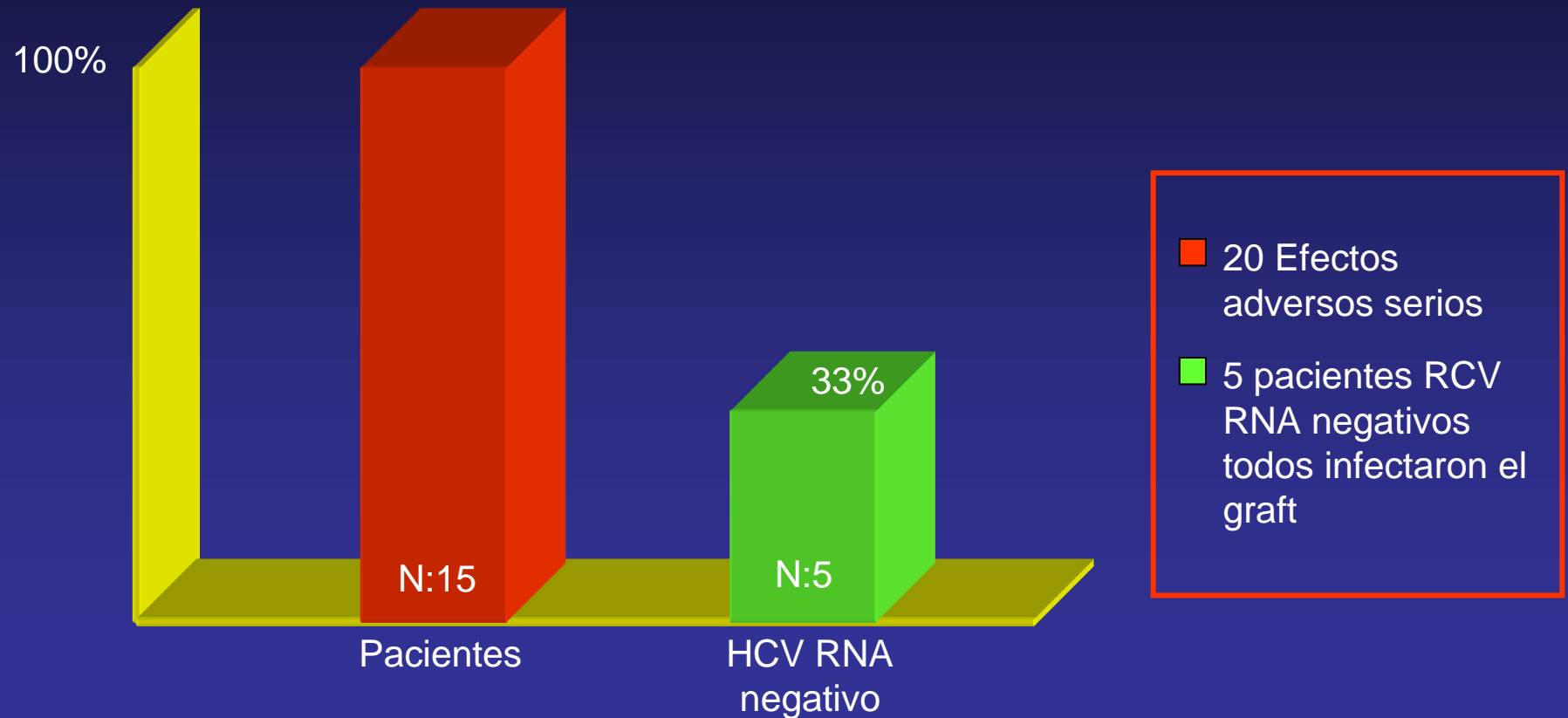
**Incremento del número de retrasplantes**

# PROGRESION DE LA FIBROSIS EN PACIENTES TRASPLANTADOS Y NO TRASPLANTADOS



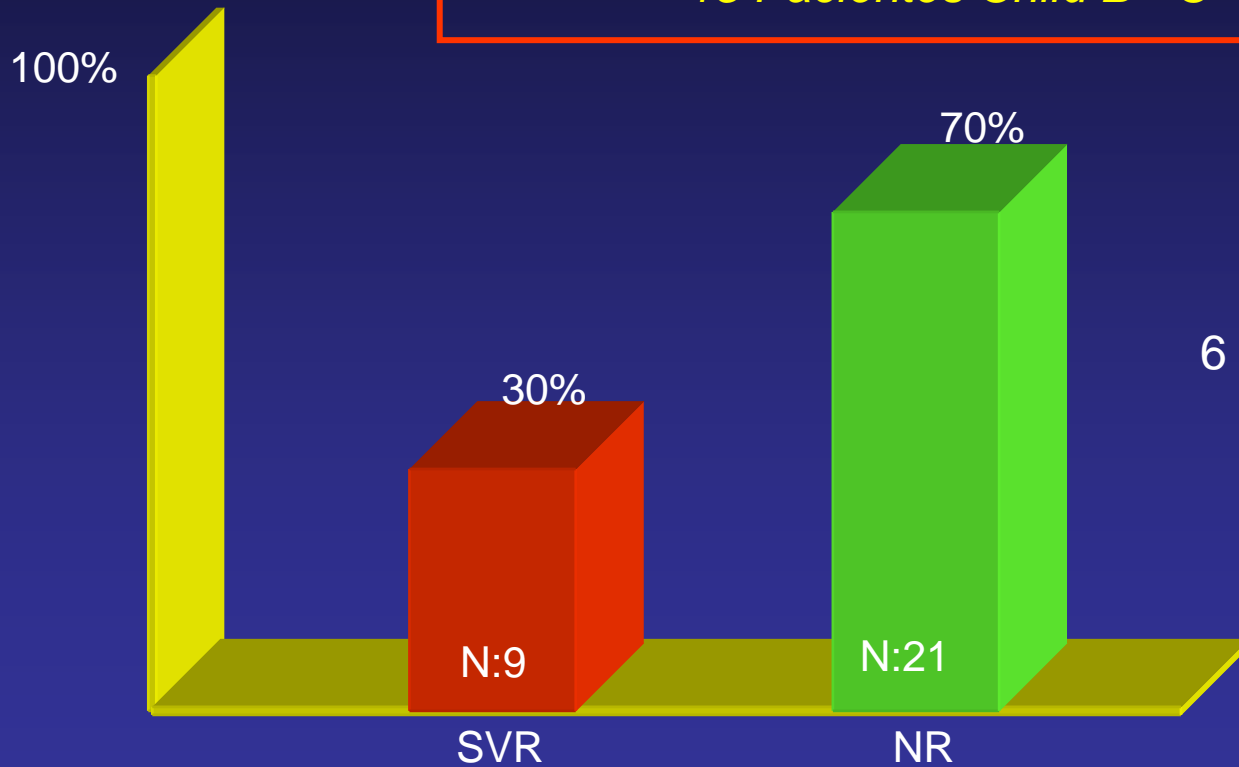
Intervalo de la infección a la cirrosis } \* 20-40 años en no trasplantados  
\* 9-12 años en trasplantados

# ESTUDIO PILOTO SOBRE TOLERABILIDAD Y EFICACIA EN EL TRATAMIENTO DE PACIENTES CON CIRROSIS POR HCV EN LISTA DE OLT



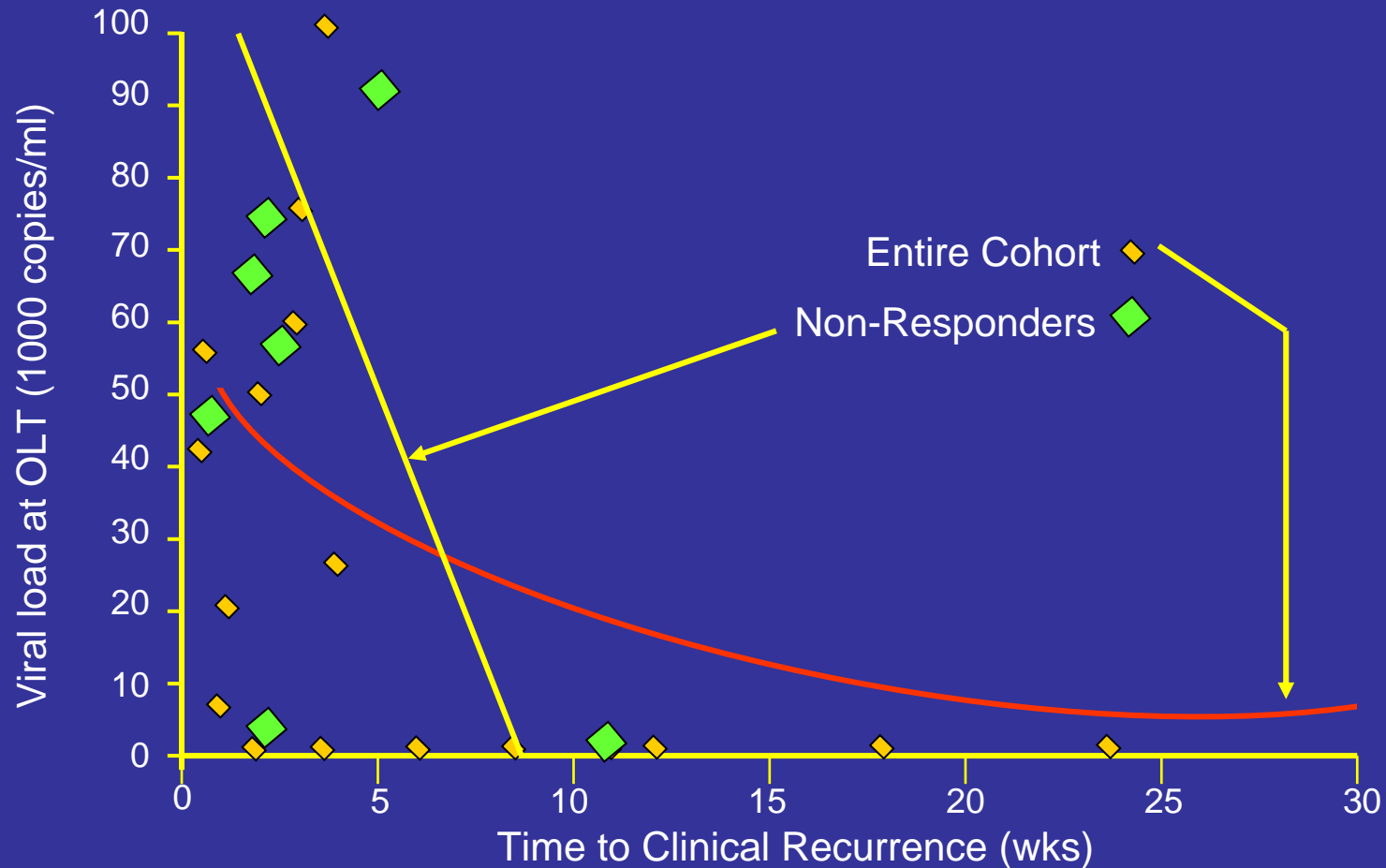
# TRATAMIENTO CON IFN ALFA 2b/RIBAVIRINA EN PACIENTES CON CIRROSIS POR HCV

15 Pacientes Child A  
15 Pacientes Child B - C

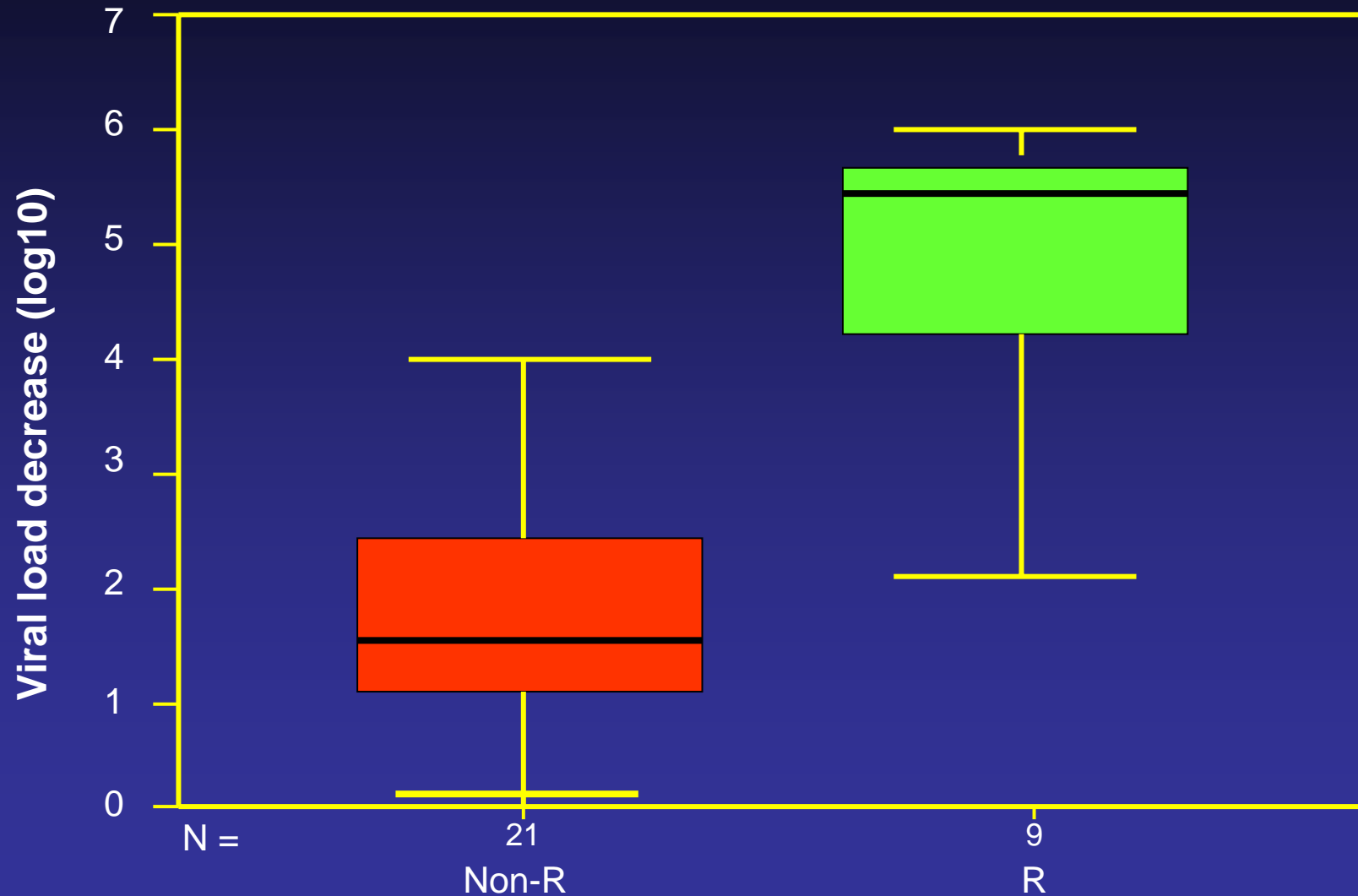


6 pacientes SVR  $\rightarrow$  46W  
Libres de infección al graft

# RELATIONSHIP OF PATIENT VIRAL LOAD AT THE TIME OF ORTHOTOPIC LIVER TRANSPLANTATION TO THE TIME OF CLINICAL RECURRENCE IN THE ENTIRE CIRRHOTIC HVC PATIENTS



# DECREASE IN VIRAL LOAD DURING TREATMENT IN RESPONDERS AND NON-RESPONDERS TO ANTIVIRAL THERAPY



# CLINICAL AND HEMATOLOGICAL ADVERSE EVENTS IN HCV- INFECTED PATIENTS AWAITING LT WHILE ON THERAPY

## Clinical Adverse events

---

Hepatic encephalopathy	3 (10%)
Ascites	2 (7%)
Variceal hemorrhage	1 (3%)
Fever	5 (17%)
Asthenia	5 (17%)
Infection <sup>a</sup>	4 (13%)
Rash	2 (7%)
Diarrhea	2 (7%)
Other <sup>b</sup>	2 (7%)

## Hematological adverse events

---

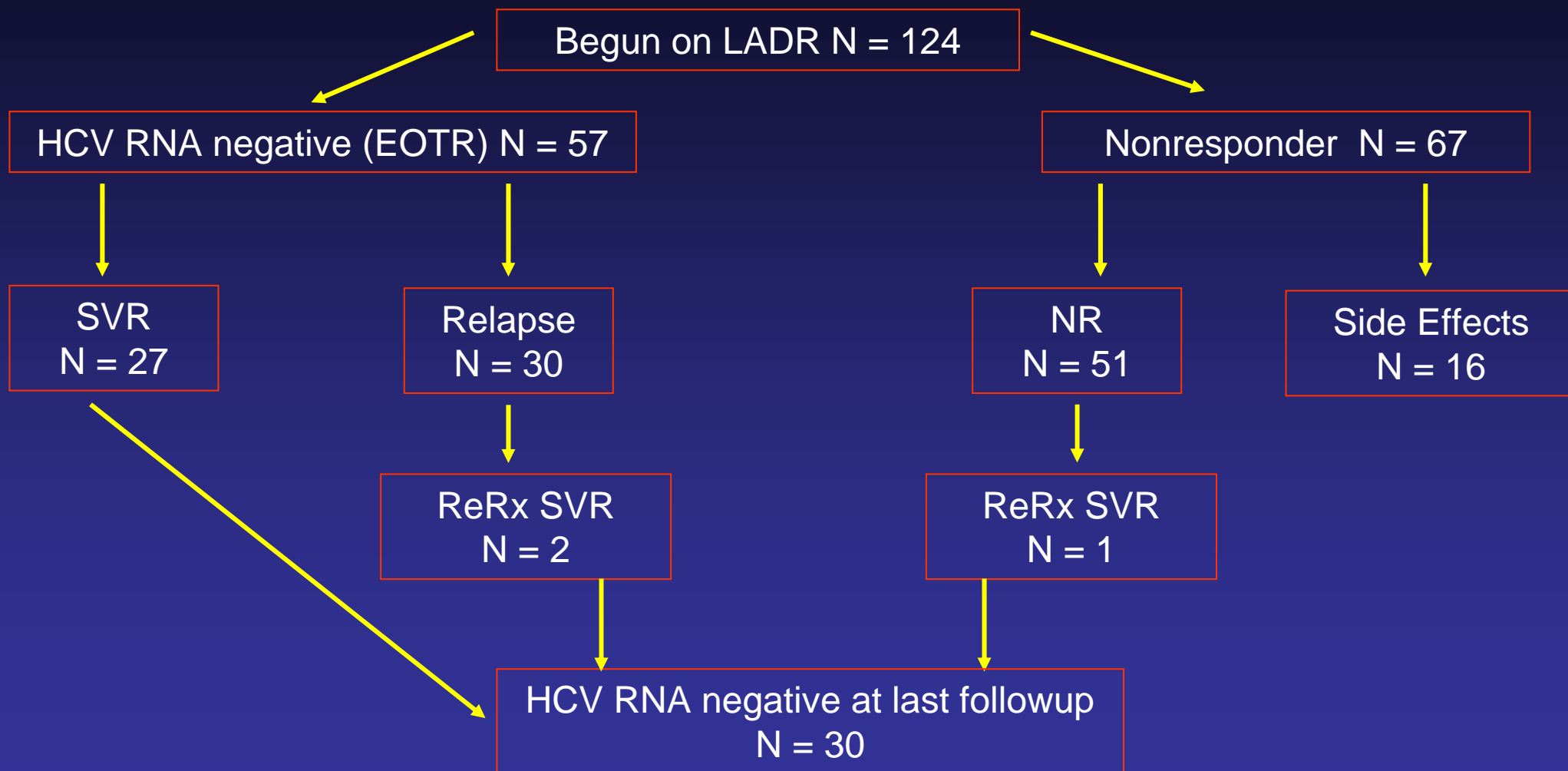
Neutropenia	18 (60%)
Thrombocytopenia	15 (50%)
Anemia	8 (27%)

---

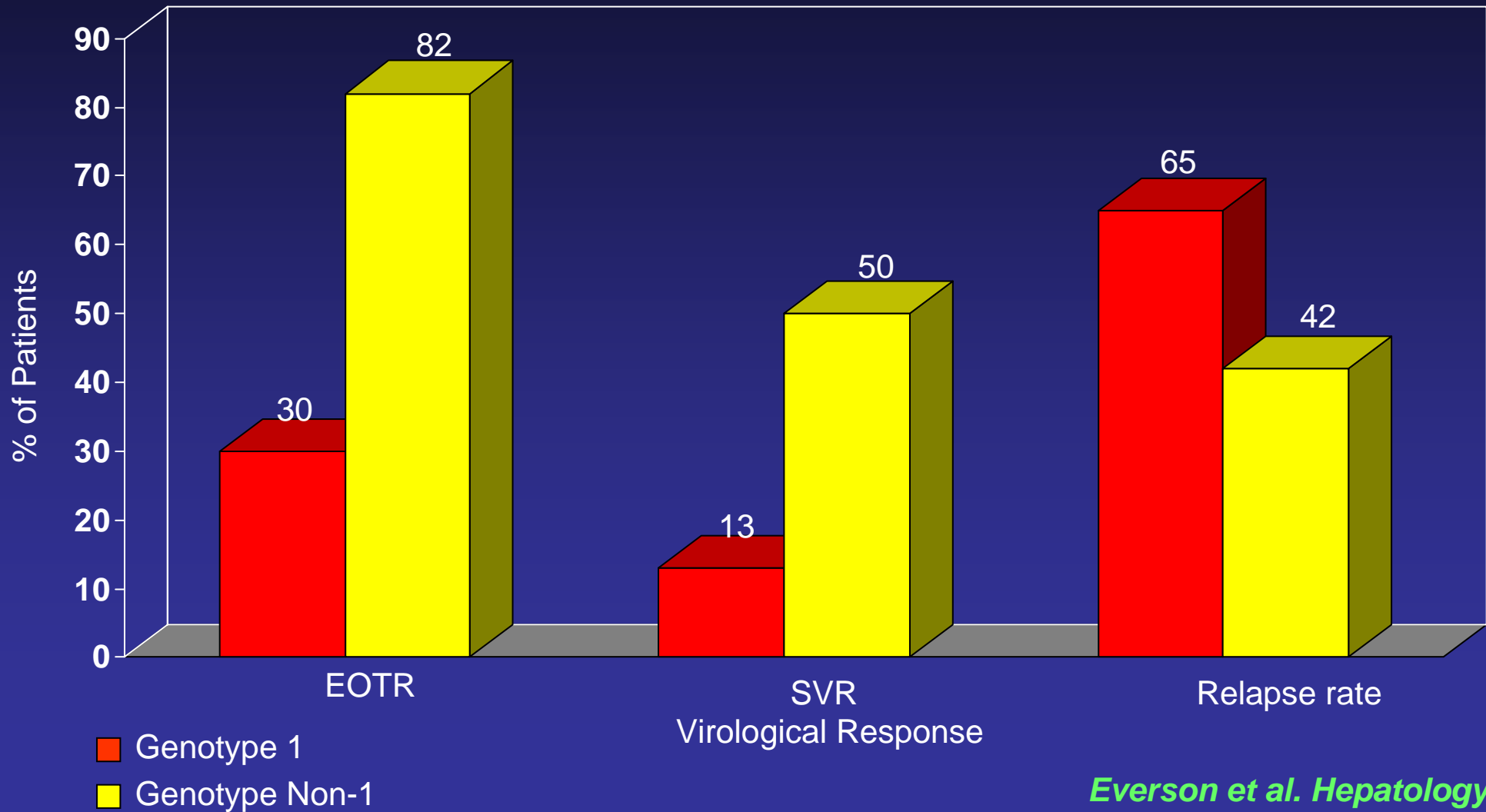
<sup>a</sup> Two patients developed sepsis

<sup>b</sup> One patient presented ALT elevation (>5 times above the upper normal limit) and one patient presented gingival hemorrhage

# THE OUTCOME OF 124 PATIENTS TREATED WITH LOW ACCELERATING DOSAGE REGIMEN (LADR)



# HCV GENOTYPE IN THE VIROLOGICAL RESPONSE TO LADR

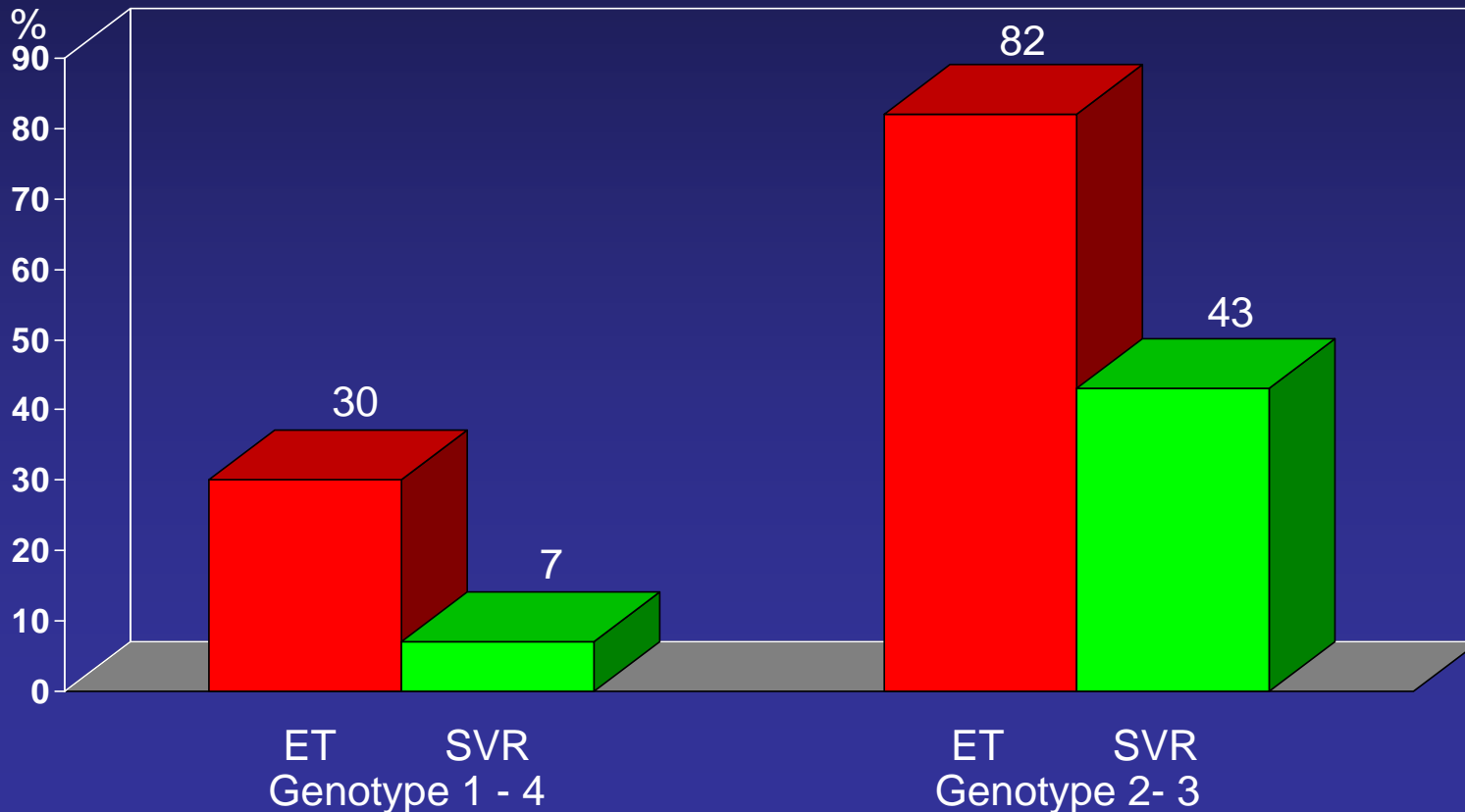
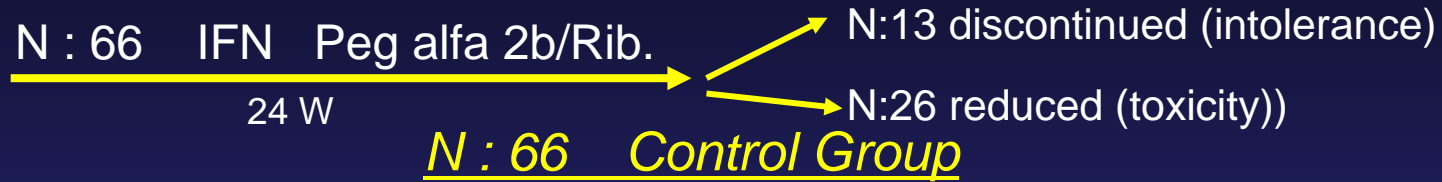


# RECURRENCE OF HCV RNA AFTER LIVER TRANSPLANTATION

## Posttransplantation

<i>Pretransplantation</i>	<i>RNA-positive</i>	<i>RNA-negative</i>	<i>Totals</i>
RNA-positive	32	0	32
DDLT	28	0	28
LDLT	4	0	4
RNA-negative	3	12	15
DDLT	3	6	9
LDLT	0	6	6
Totals	35	12	47

# PEGINTERFERON ALFA-2b AND RIBAVIRIN IN PATIENTS WITH HEPATITIS C VIRUS AND DECOMPENSATED CIRRHOSIS: A CONTROLLED STUDY



# SEVERE INFECTION DURING THE STUDY

**O.R.**

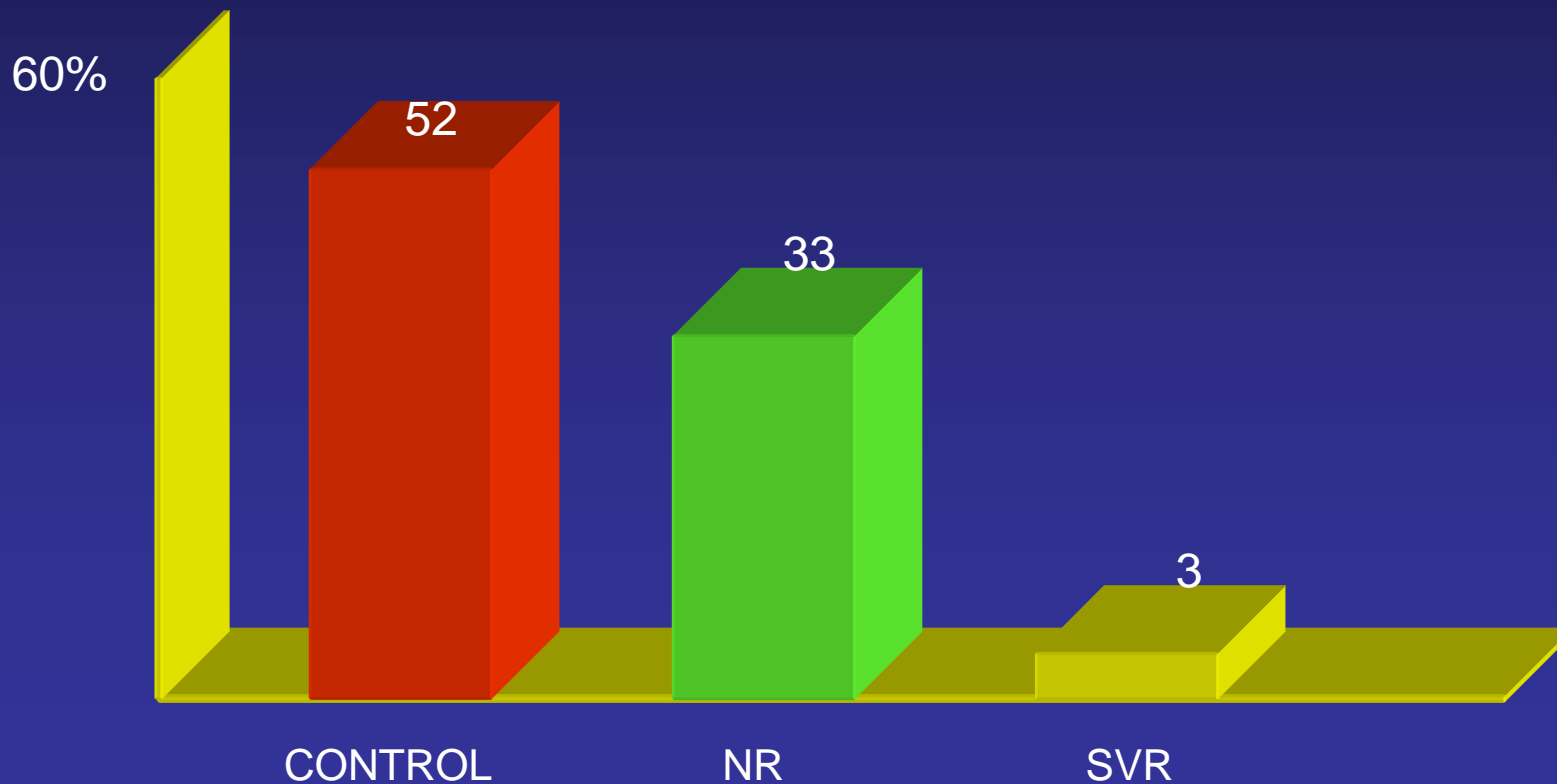
**2.95**

**1.97**

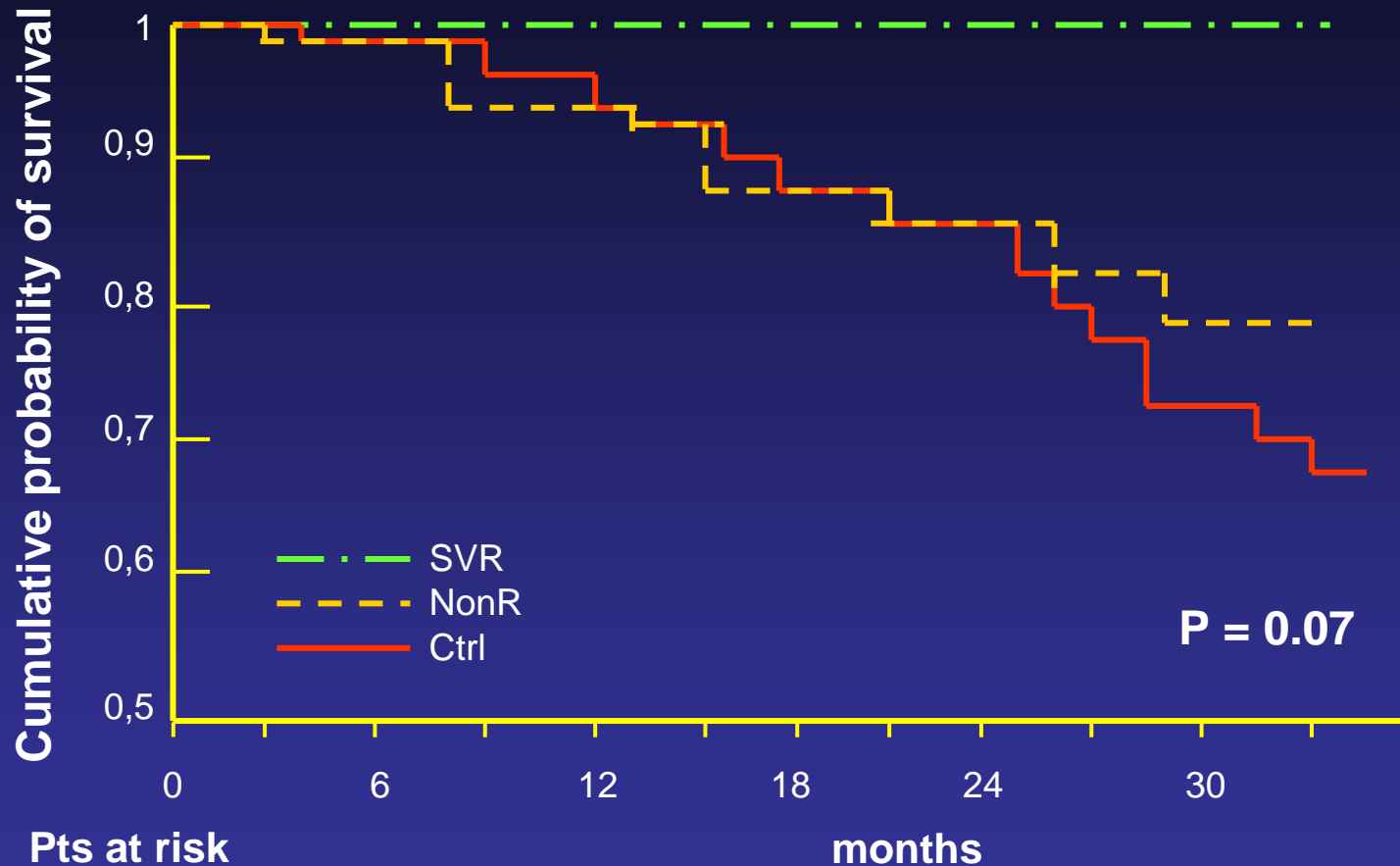
**Treated**

**Control**

## DESCOMPENSATED EVENTS IN THE FOLLOW UP



# OVERALL SURVIVAL IN RESPONDERS, NON-RESPONDERS, AND UNTREATED PATIENTS



	0	6	12	18	24	30	36
SVR	13	13	13	13	13	13	13
Non R	48	47	45	43	40	40	24
Ctrl	59	58	57	52	48	48	33

# INHIBIDORES DE LAS ENZIMAS VIRALES

Proteasa

Helicasa

Polimerasa

Monoterapia o  
combinados



? eficientes

Cirrosis HCV  
Descompensada

Hepatitis HCV  
Posttrasplante

# RESUMEN

- 1) Las terapéuticas actuales para pacientes con Cirrosis HCV no tienen el tiempo suficiente para poder ser evaluadas a largo plazo
- 2) En pacientes con SVR parecieran disminuir las complicaciones y el riesgo del HC, aumentando la sobrevida
- 3) En pacientes con cirrosis HCV descompensada los efectos severos son muy frecuentes, obligando a reducir la dosis resultando la SVR escasa, en especial al genotipo I
- 4) El principal objetivo es el de llevar al paciente al trasplante sin RNA HCV disminuyendo así el riesgo de infección del injerto
- 5) Es probable que los inhibidores de las enzimas virales puedan ser útiles. La combinación de fármacos pareciera una opción probable.