Manejo de la Infección por VHC

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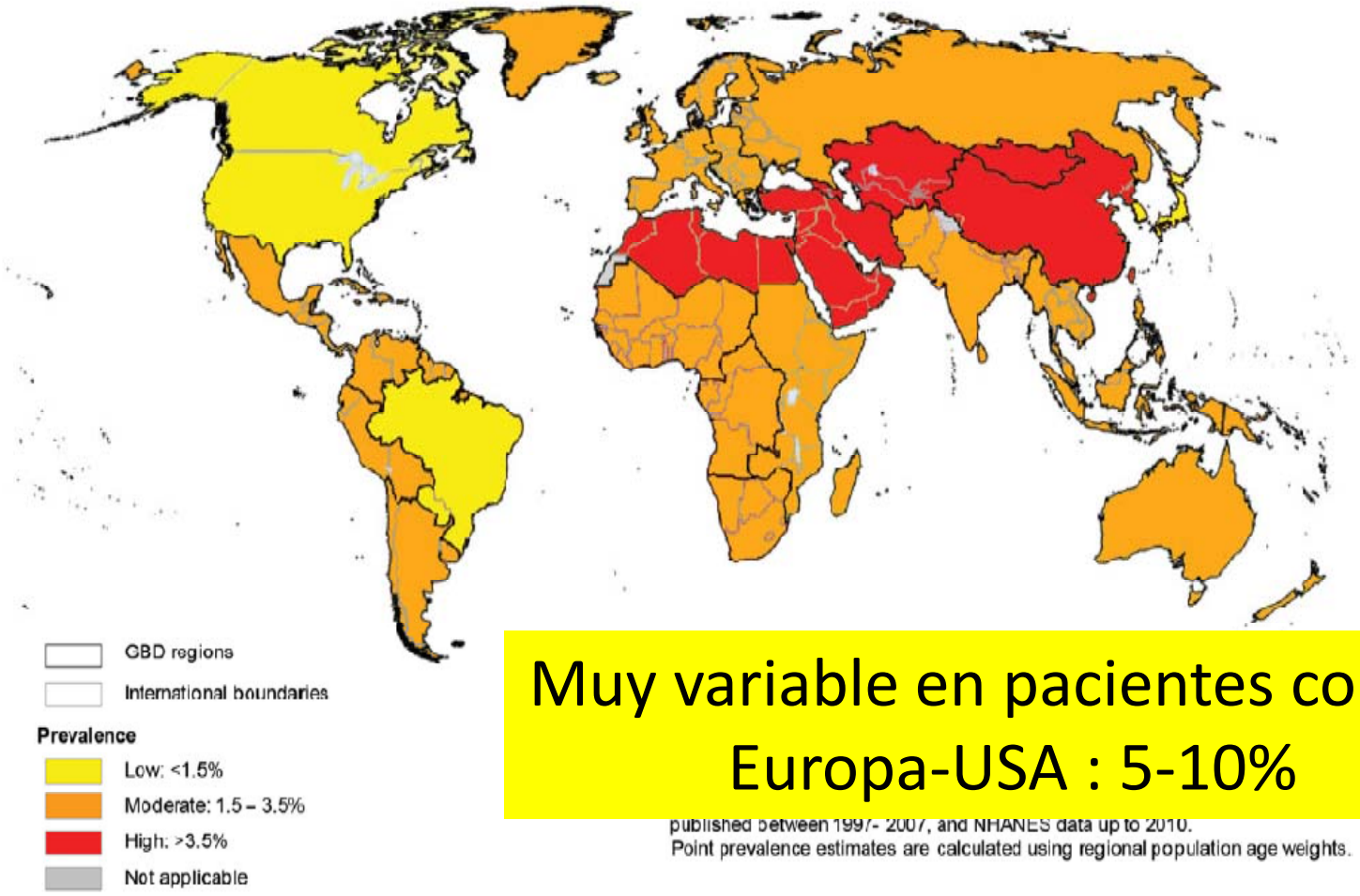
Unidad de Hepatología. Servicio de Medicina Interna CHUS

Prevalencia de la infección por VHC en el mundo

La prevalencia ha aumentado de 2.3% a 2.8%



published between 1997- 2007, and NHANES data up to 2010.
Point prevalence estimates are calculated using regional population age weights.

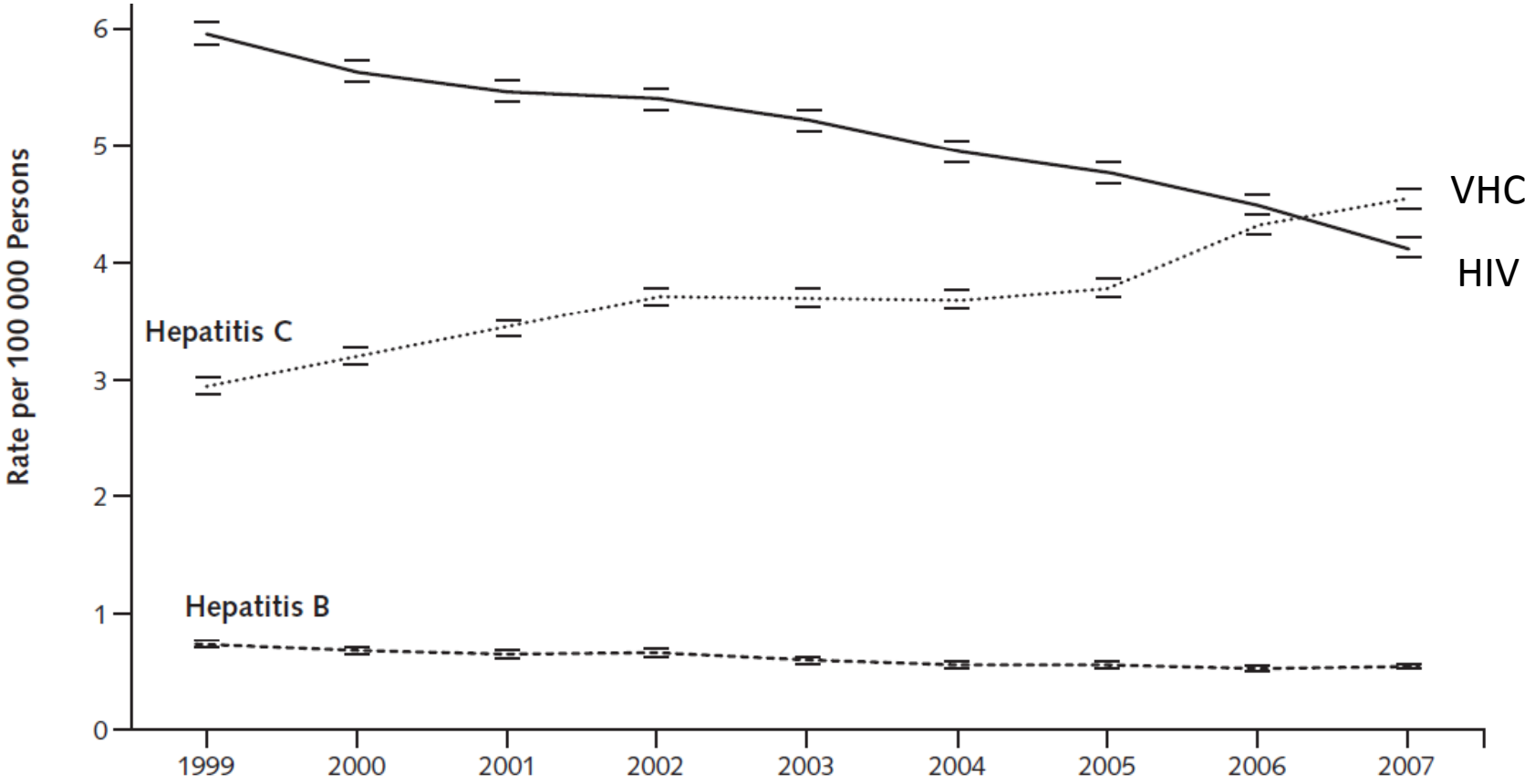
Muy variable en pacientes con HD
Europa-USA : 5-10%

Hanafiah, Hepatology april 2013

Annals of Internal Medicine | ORIGINAL RESEARCH

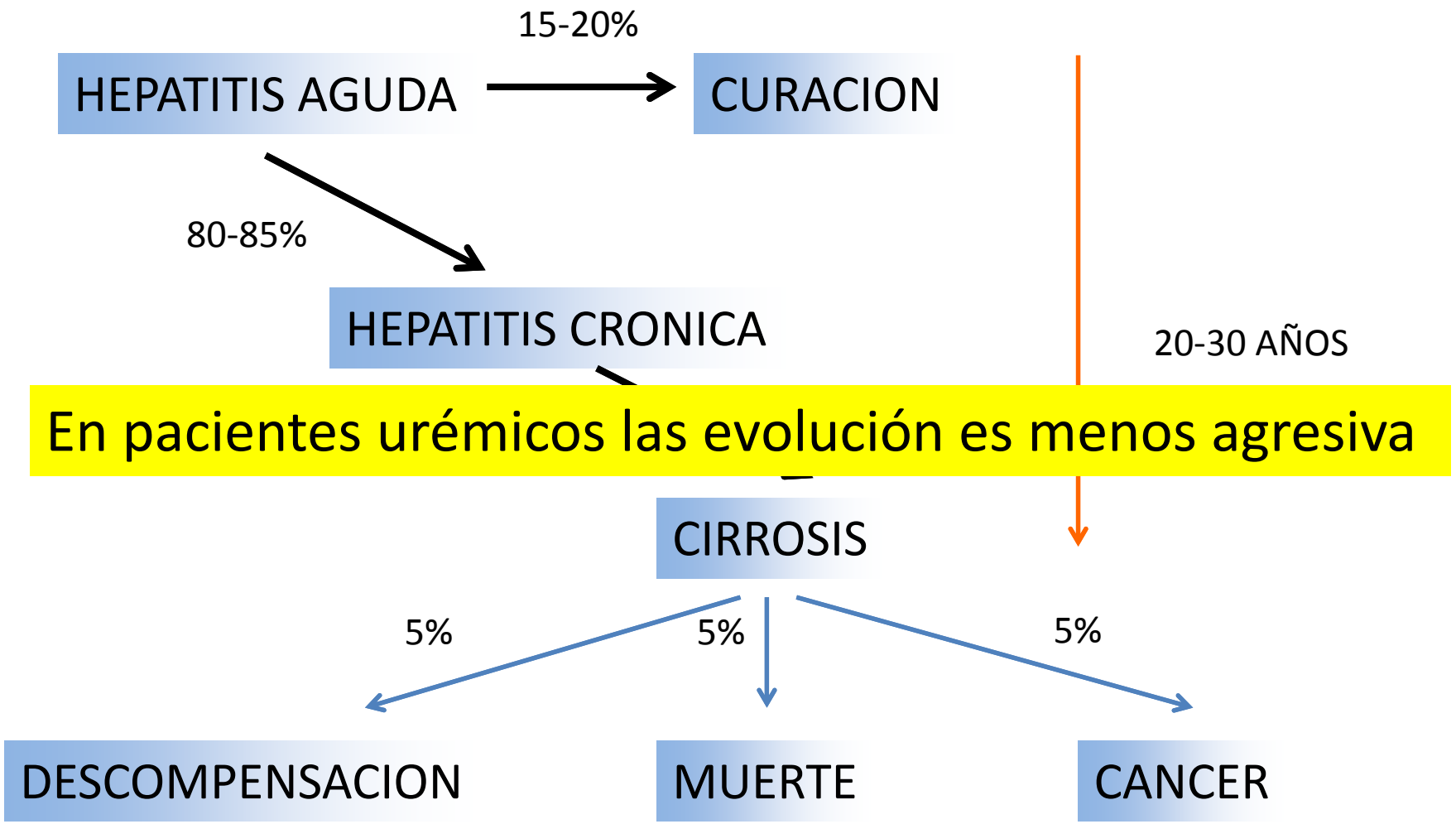
The Increasing Burden of Mortality From Viral Hepatitis in the United States Between 1999 and 2007

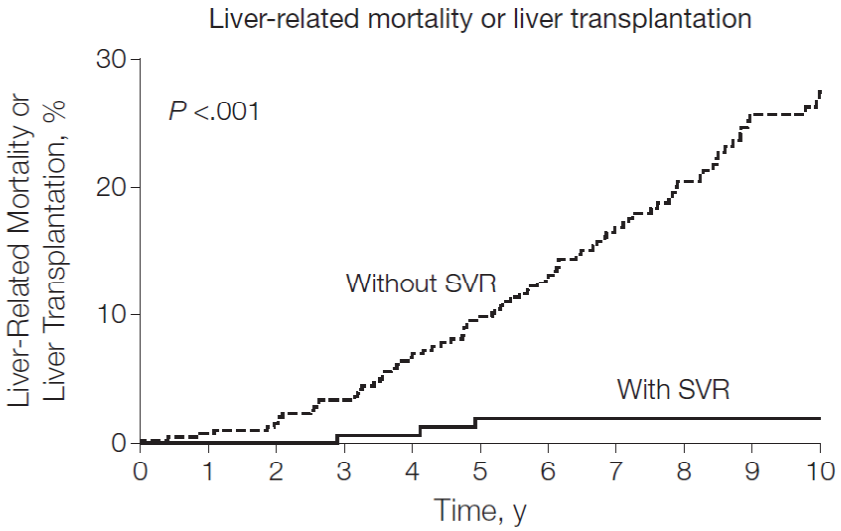
Kathleen N. Ly, MPH; Jian Xing, PhD; R. Monina Klevens, DDS, MPH; Ruth B. Jiles, PhD, MPH; John W. Ward, MD; and Scott D. Holmberg, MD, MPH

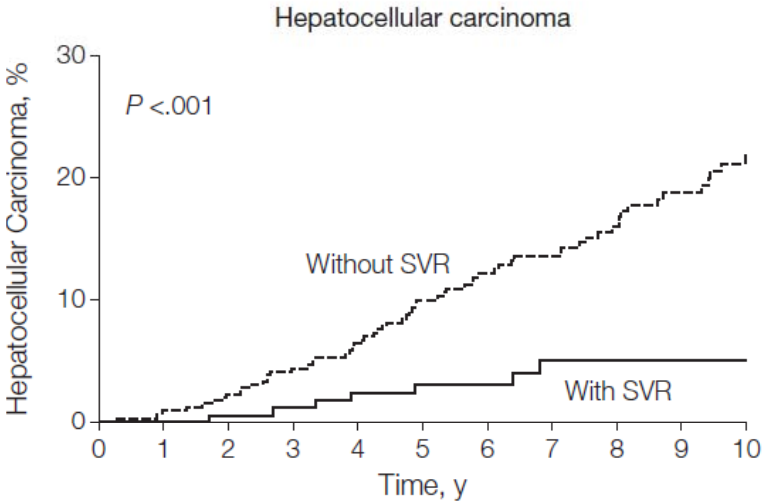


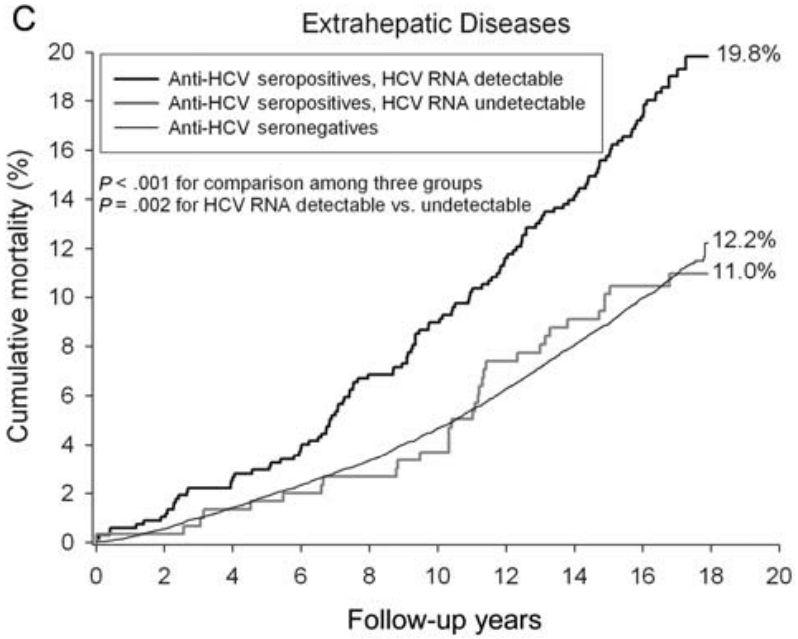
Ann Inter Med, 2012

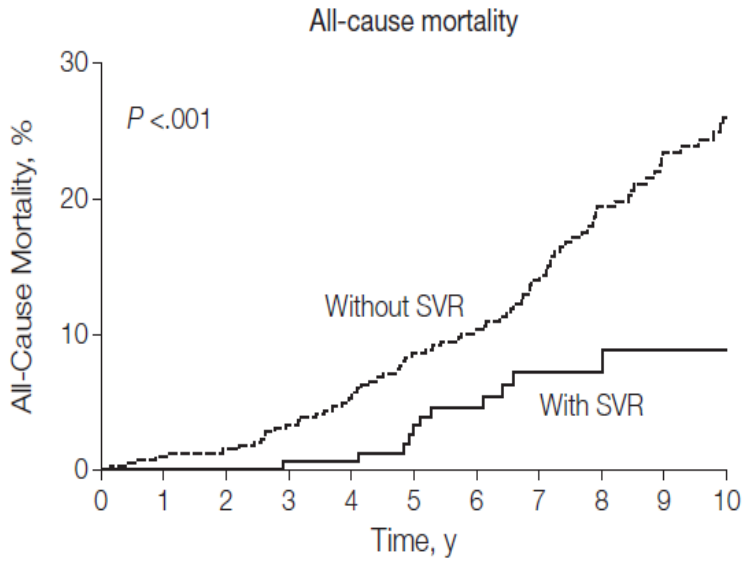
HISTORIA NATURAL DE LA INFECCION POR VHC











Lee, J infect Dis 2012

Van de Meer
JAMA 2012

Antiviral Treatment for Hepatitis C Virus Infection Is Associated With Improved Renal and Cardiovascular Outcomes in Diabetic Patients

Yao-Chun Hsu,[1,2] Jaw-Town Lin,[2,3,4] Hsiu J. Ho,[3] Yu-Hsi Kao,[5] Yen-Tsung Huang,[6] Nai-Wan Hsiao,[7] Ming-Shiang Wu,[8] Yi-Ya Liu,[9] and Chun-Ying Wu[1,9,10,11,12]

HEPATOLOGY, Vol. 59, No. 4, 2014

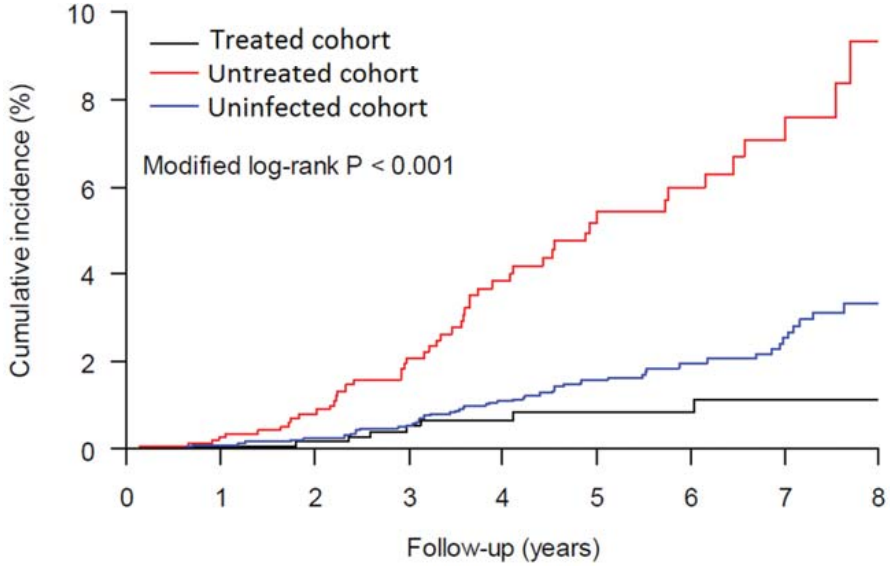


Fig. 2. Cumulative incidence of ESRD in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event.

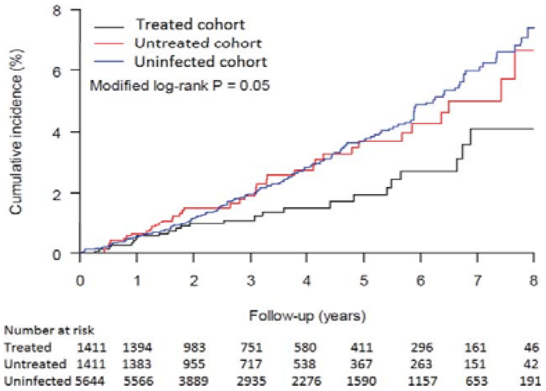


Fig. 4. Cumulative incidence of acute coronary event in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event.

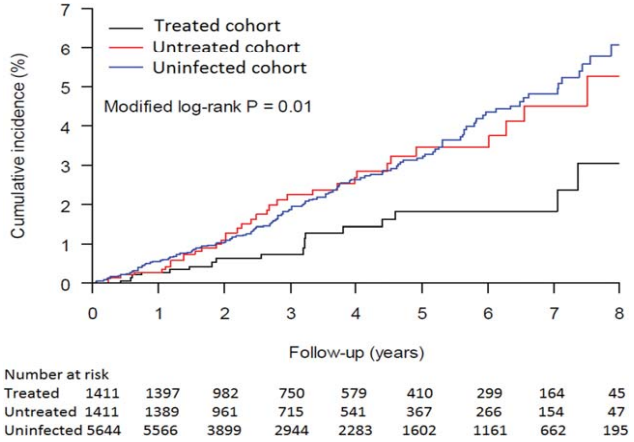


Fig. 3. Cumulative incidence of ischemic stroke in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event.

Mortalidad asociada a VHC en HD

of Dialysis[ ] predictor of all-cause mortality (95%CI: 1.15-1.62, *P* = 0.003)

Kidney Diseases Associated with Hepatitis C Infection

Native Kidneys

- Mixed cryoglobulinemia (MC)
- MPGN
- Membranous nephropathy
- Fibrillary glomerulonephritis

After Transplantation

- *De novo* or recurrent MPGN
- Membranous nephropathy
- Acute transplant glomerulopathy
- Renal thrombotic microangiopathy
- Chronic transplant glomerulopathy
- Liver Transplantation
- MC with or without MPGN

Baid S, et al. Transplantation 2000;70:255-61

HCV Infection and Kidney Disease

University of Wisconsin

- Analysis of 1,368 cadaver kidney transplants from 1991-2001

D-/R-	1,139
D-/R+	43
D+/R-	115
D+/R+	71

S. Tome and Julio Pascual Transplantation reviews 2007

HCV Infection and Kidney Disease

University of Wisconsin

D+/R- Policy

- HCV donor positive kidneys used only in high-risk recipients
  - Type II diabetics
  - High cardiovascular risk
  - Lack of dialysis access
  - High risk retransplants

Hepatitis C

Patient Deaths

University of Wisconsin 1991-2001

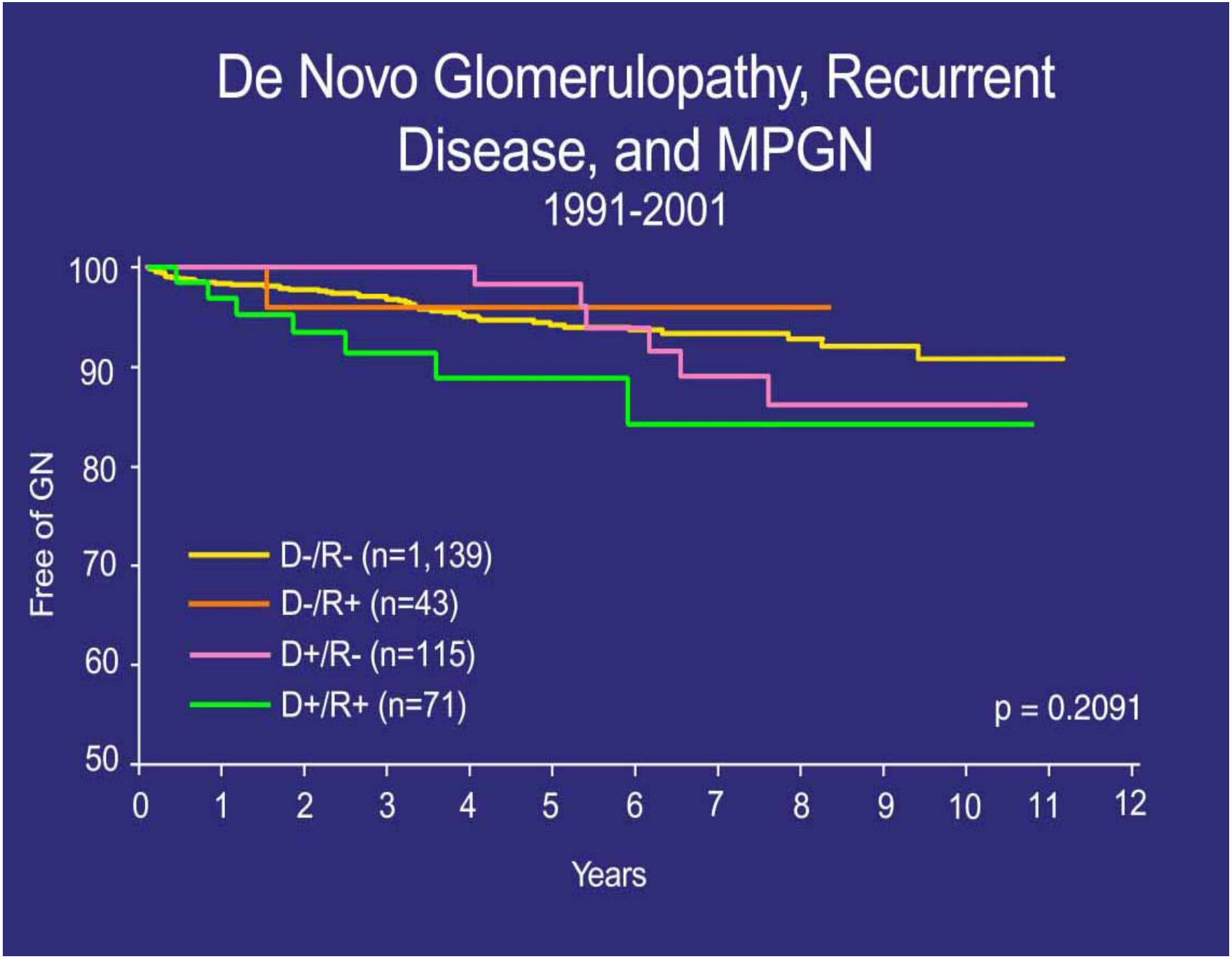
	D-/R-	**D-/R+**	**D+/R-**	**D+/R+**
N	1108	37	112	69
Total deaths	179 (16%)	7 (19%)	74 (66%)	22 (32%)

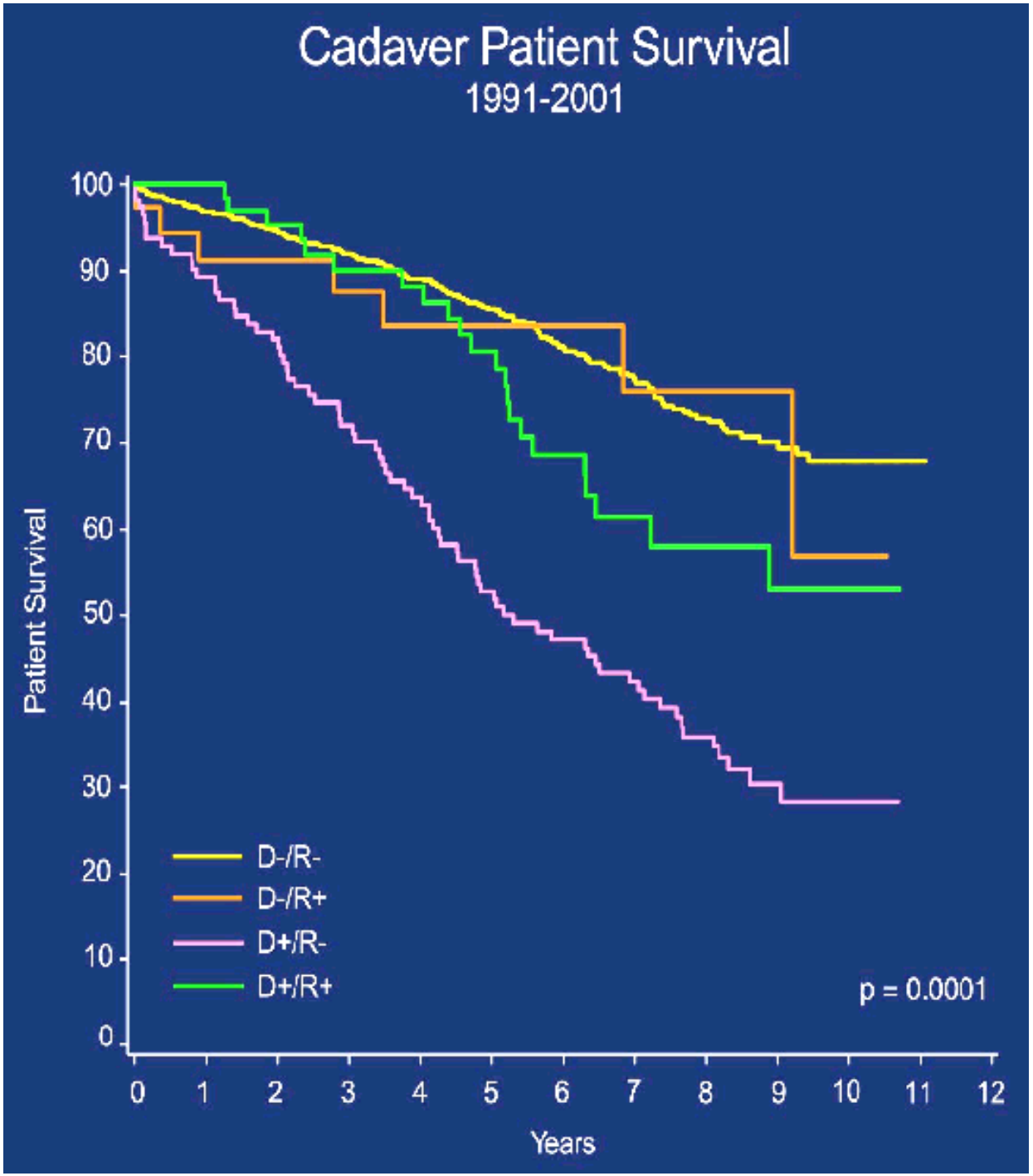
Cause of Death in Patients with Hepatitis C
University of Wisconsin 1991-2001

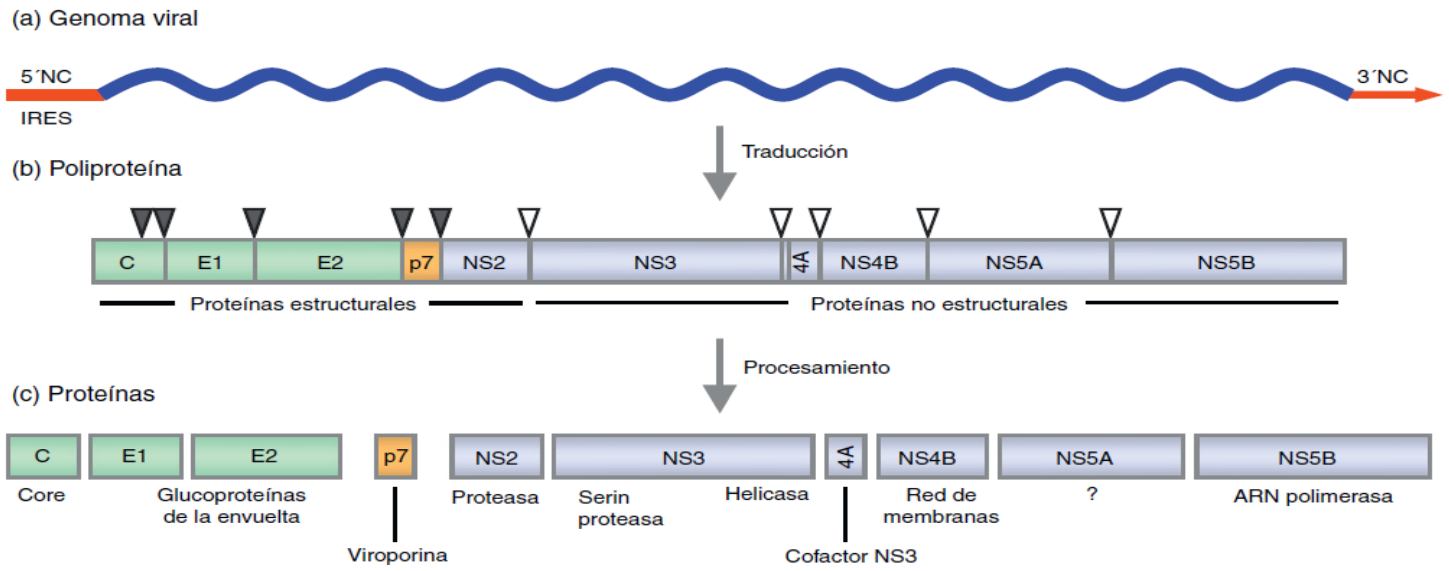
	D-/R-	D-/R+	D+/R-	D+/R+
Cardiac	50 (28%)	4 (58%)	22 (30%)	7 (32%)
Sepsis	34 (19%)	0	13 (18%)	2 (9%)
Malignancy	27 (15%)	1 (14%)	8 (11%)	5 (23%)
Liver failure	1 (1%)	1 (14%)	4 (5%)	0
Unknown	14 (8)	1 (14%)	12 (16%)	4 (18%)
PTLD	4 (2%)	0	0	0
Other	47 (27%)	0	12 (20%)*	5 (18%)†

**Embolism 1, GI bleed 1, other bleed 1, withdrawal of dialysis 6, suicide 1, aneurysm 1, respiratory arrest 1*

†GI bleed 1, other 1, peritonitis 1, pulmonary 1, respiratory arrest 1


De Novo Glomerulopathy, Recurrent Disease, and MPGN
1991-2001
Free of GN
100
90
80
70
60
50
0
1
2
3
4
5
6
7
8
9
10
11
12
Years
D-/R- (n=1,139)
D-/R+ (n=43)
D+/R- (n=115)
D+/R+ (n=71)
p = 0.2091


Cadaver Patient Survival
1991-2001
Patient Survival
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Years
D-/R-
D-/R+
D+/R-
D+/R+
p = 0.0001



- **El VHC presenta elevada heterogeneidad a nivel genómico:**
  - **6 genotipos (más de 80 subtipos)**
- **Los genotipos son clínicamente relevantes para:**
  - **La historia natural de la enfermedad**
  - **La elección del régimen de tratamiento**
  - **La respuesta al tratamiento con interferón**

Evolución de los tratamientos de la Hepatitis C

Año 1992

Interferón estándard

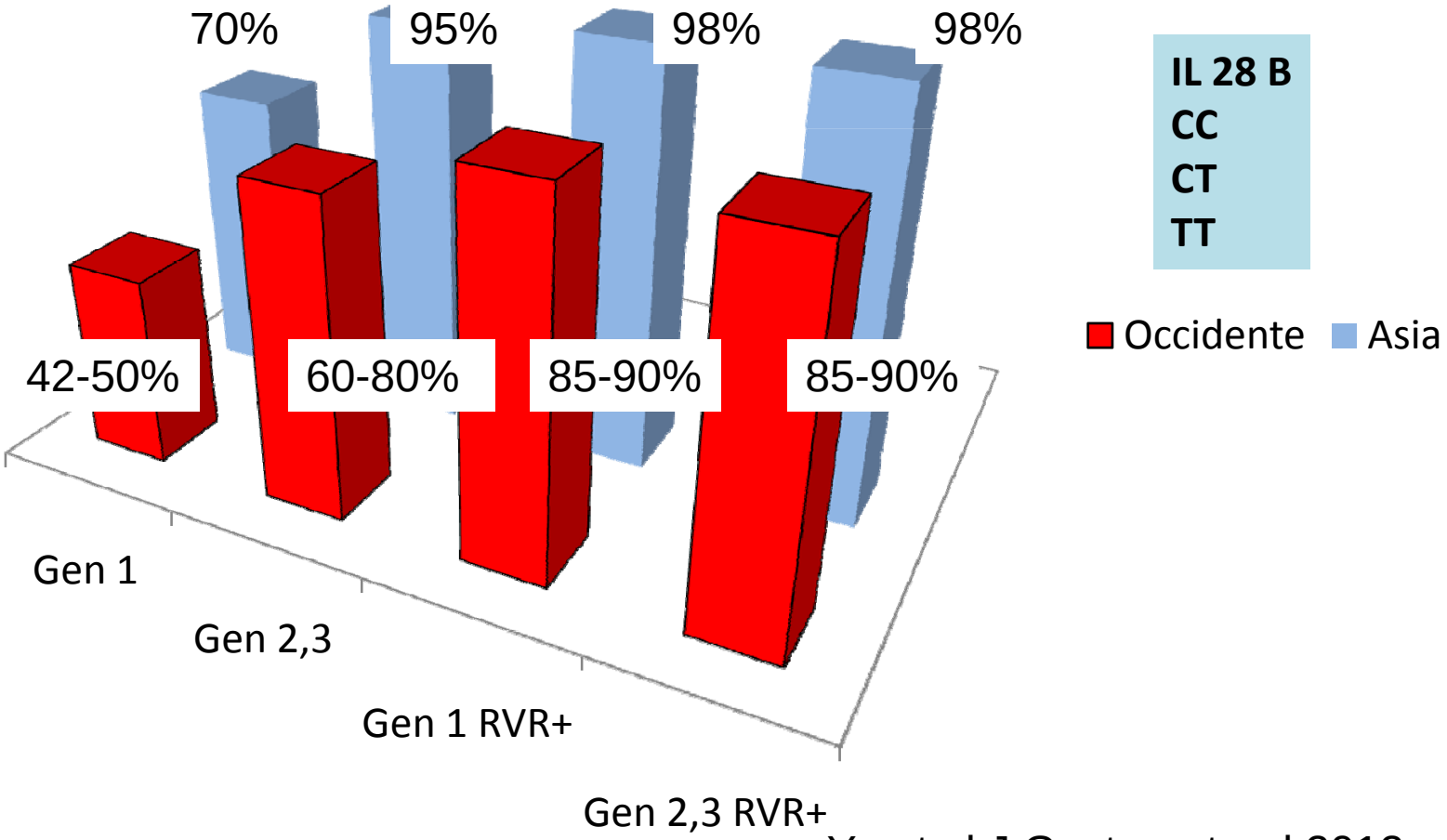
Año 1998

Ribavirina

Año 2000

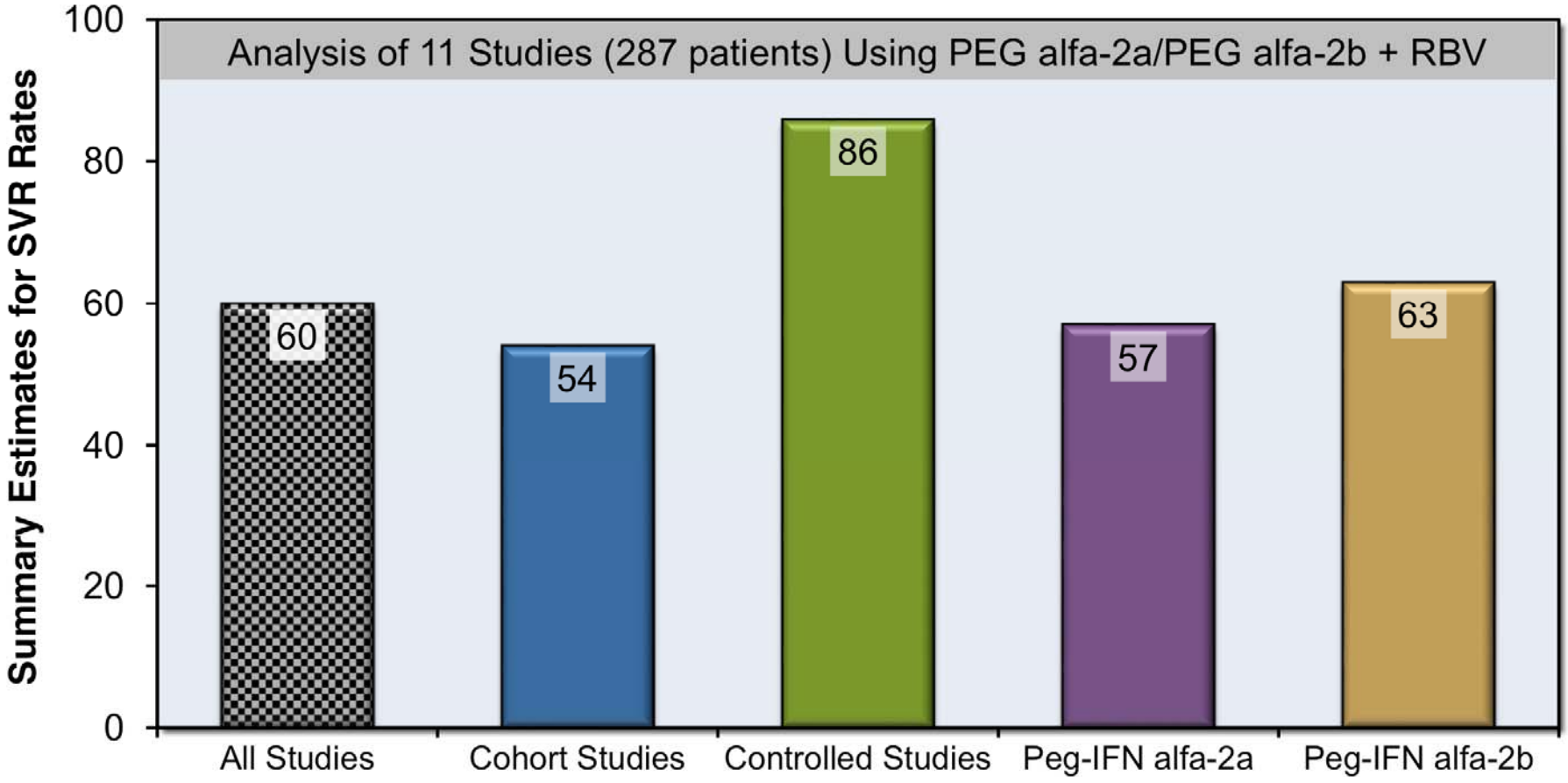
Peg Interferon

RVS VHC diferencias entre occidente y oriente



Yu et al J Gastroenterol 2012
Ghany et al Hepatology 2009

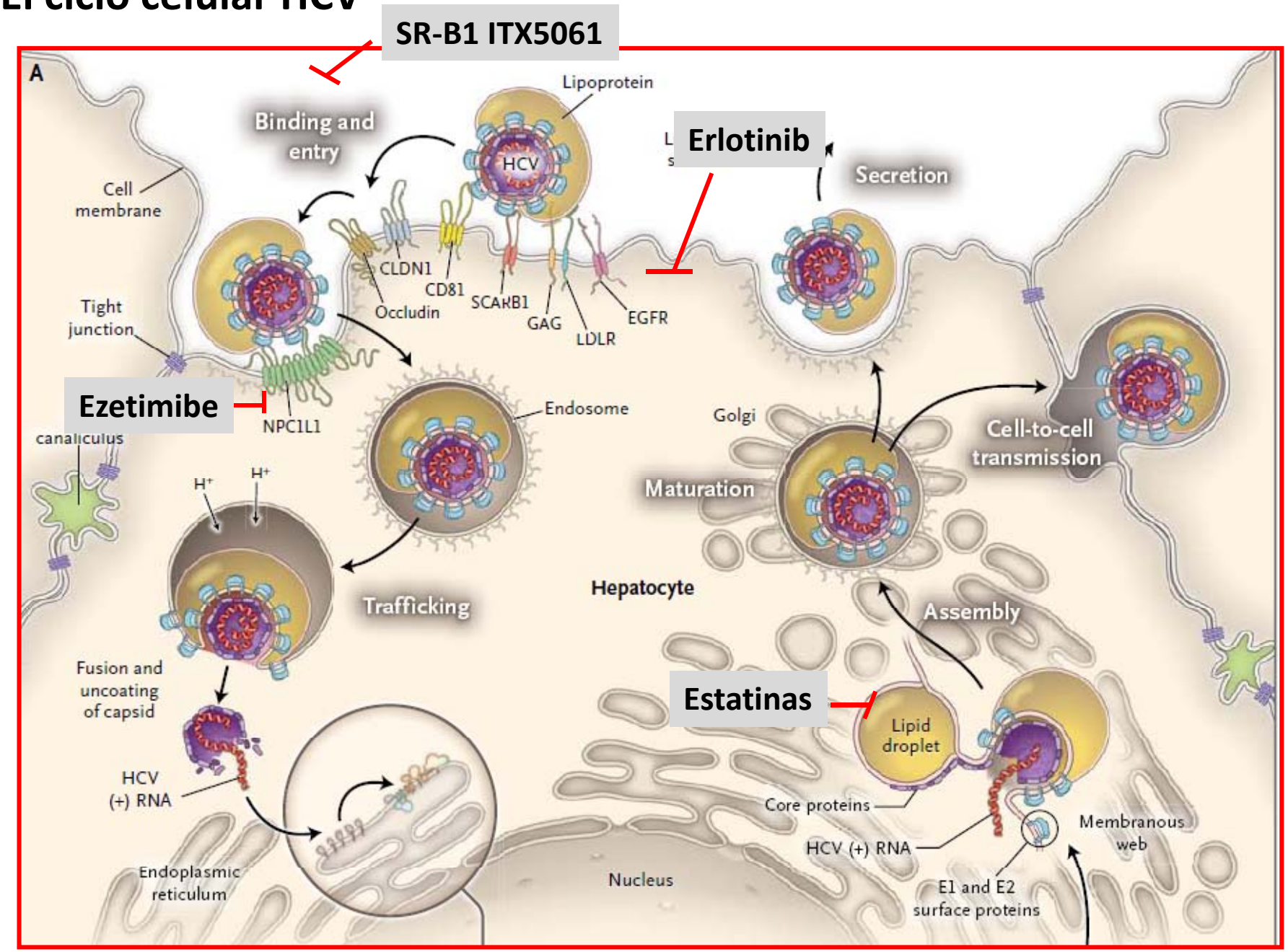
Uso de Peg Interferon y Ribavirina en Hemodialisis



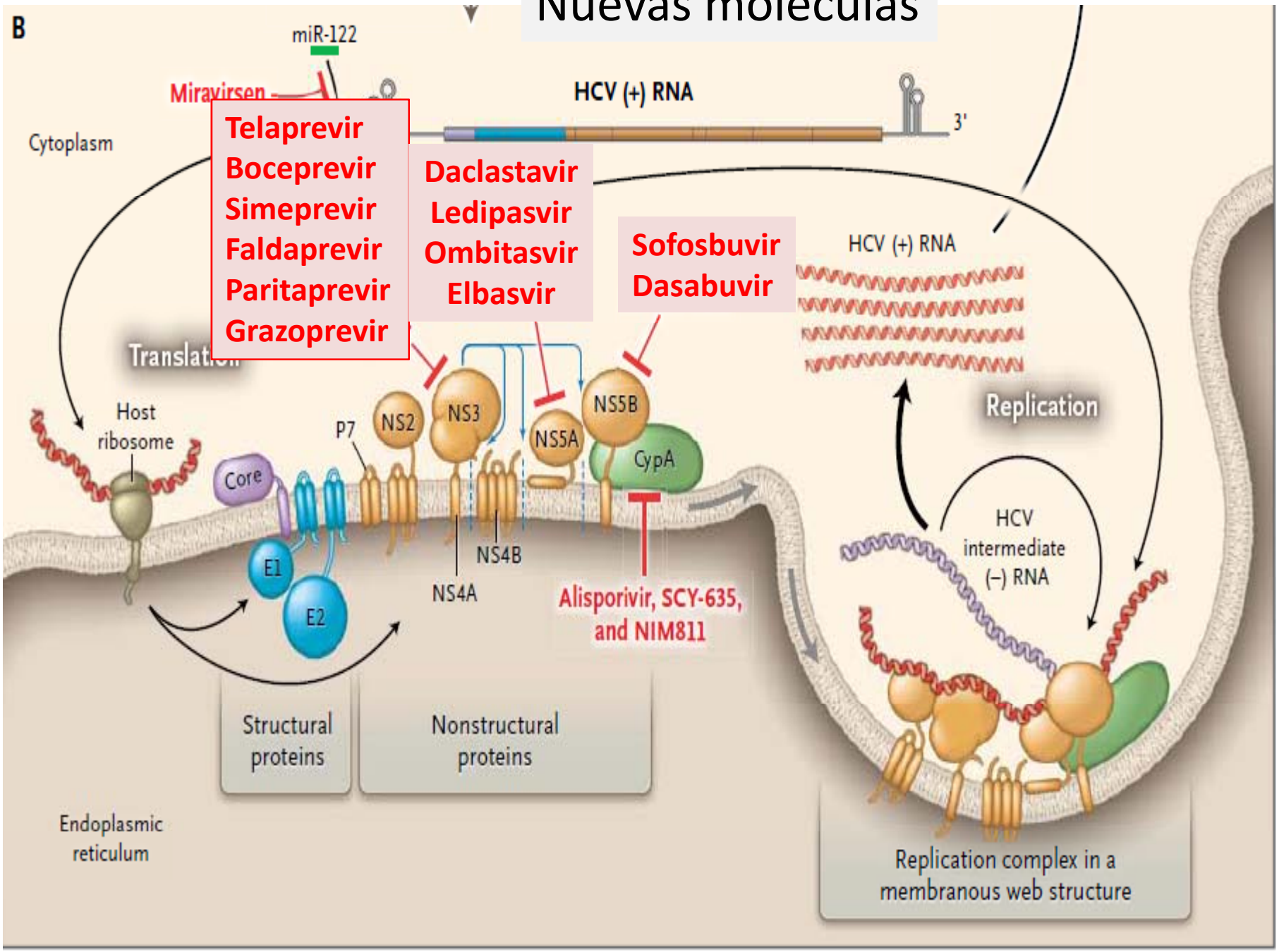
Fabrizi J, Viral Hepat 2014

El ciclo del virus

El ciclo celular HCV



Nuevas moleculas



Regímenes de tratamiento libres de Interferón

Sofosbuvir + RVB

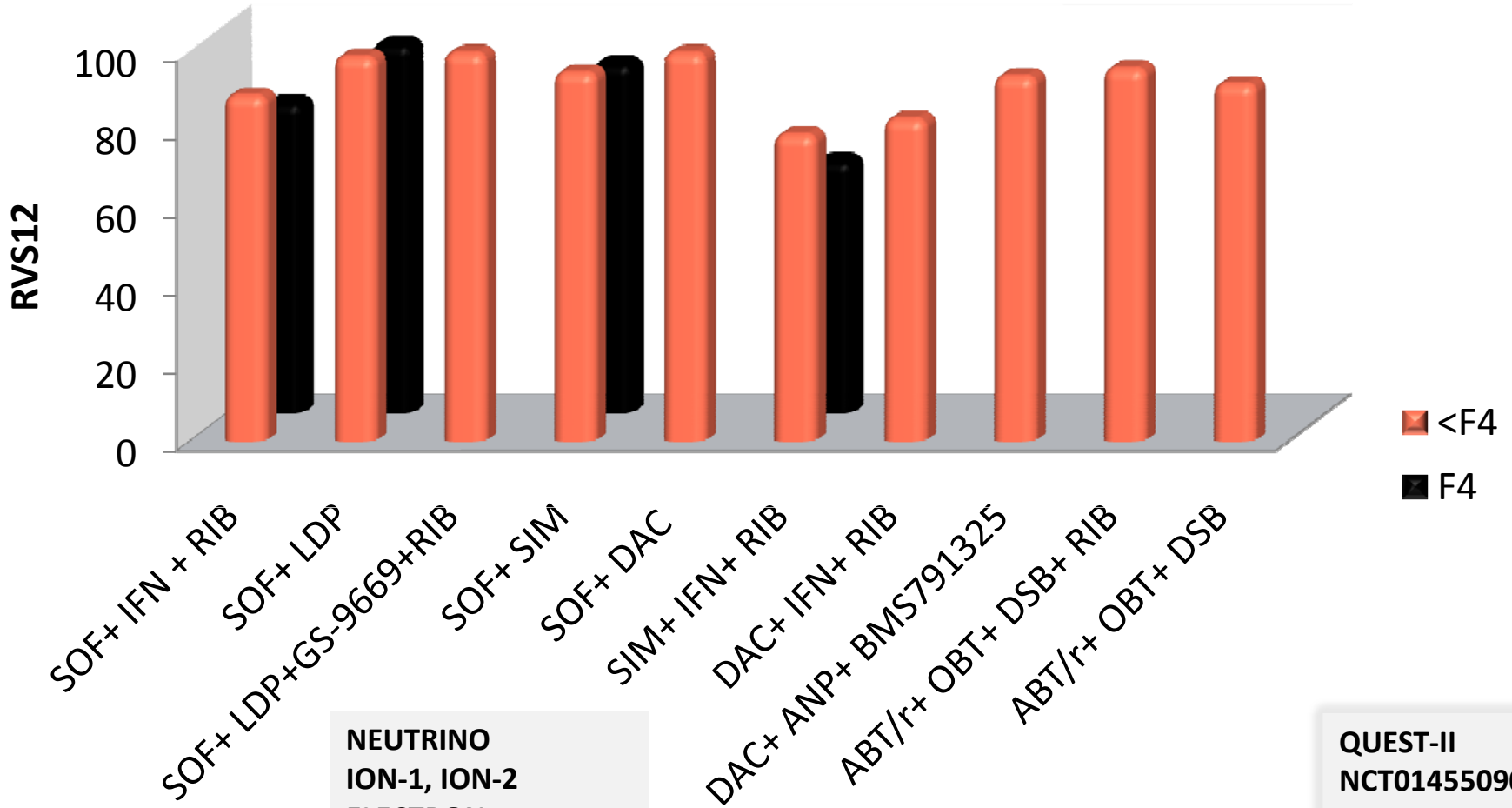
Sofosbuvir + Ledipasvir +/- RBV

PTV/r/OBT/ SBV+/- RVB

Sofosbuvir + DCV

GENOTIPO 1

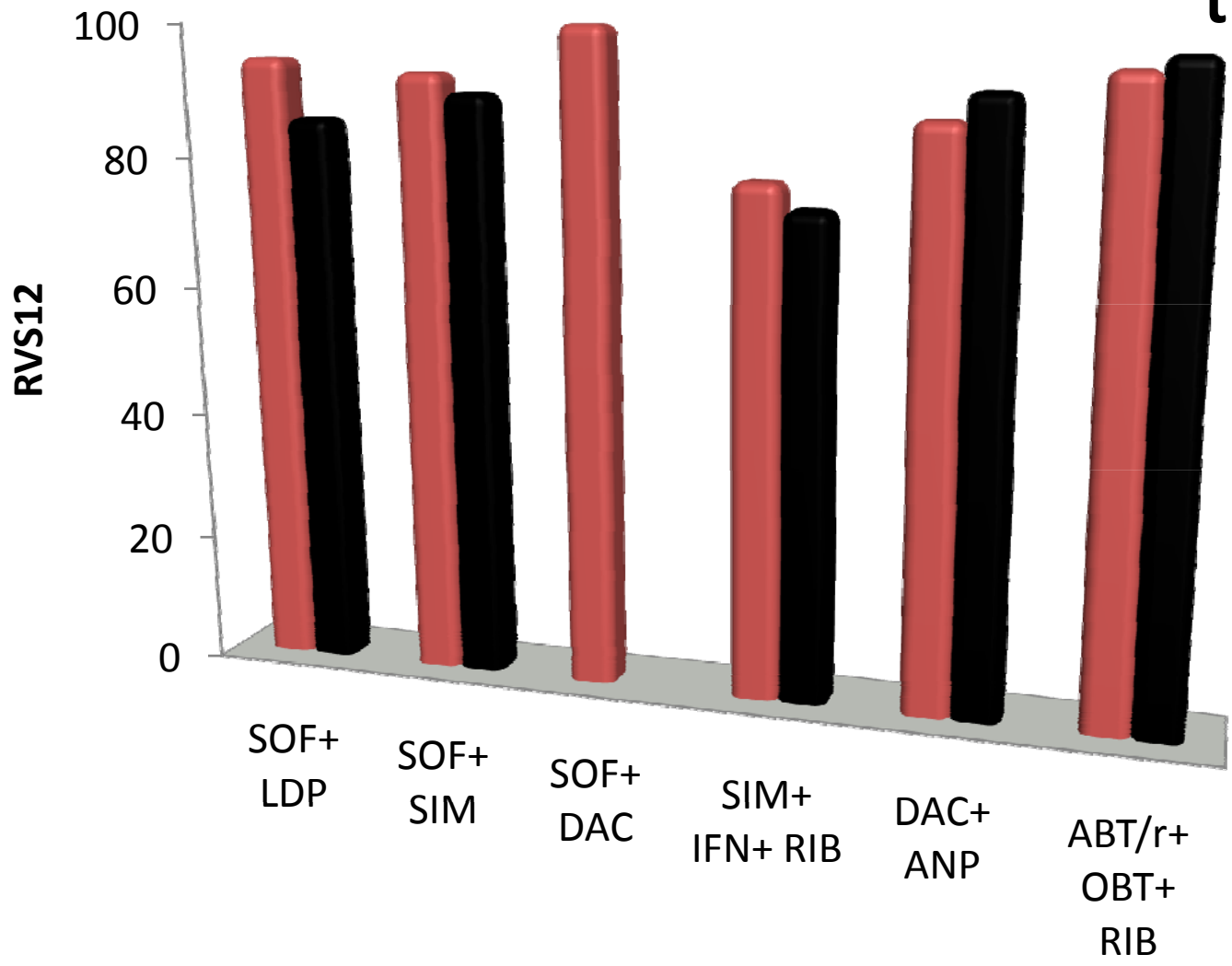
NAIVE



NEUTRINO
ION-1, ION-2
ELECTRON
COSMOS
NCT01359644C

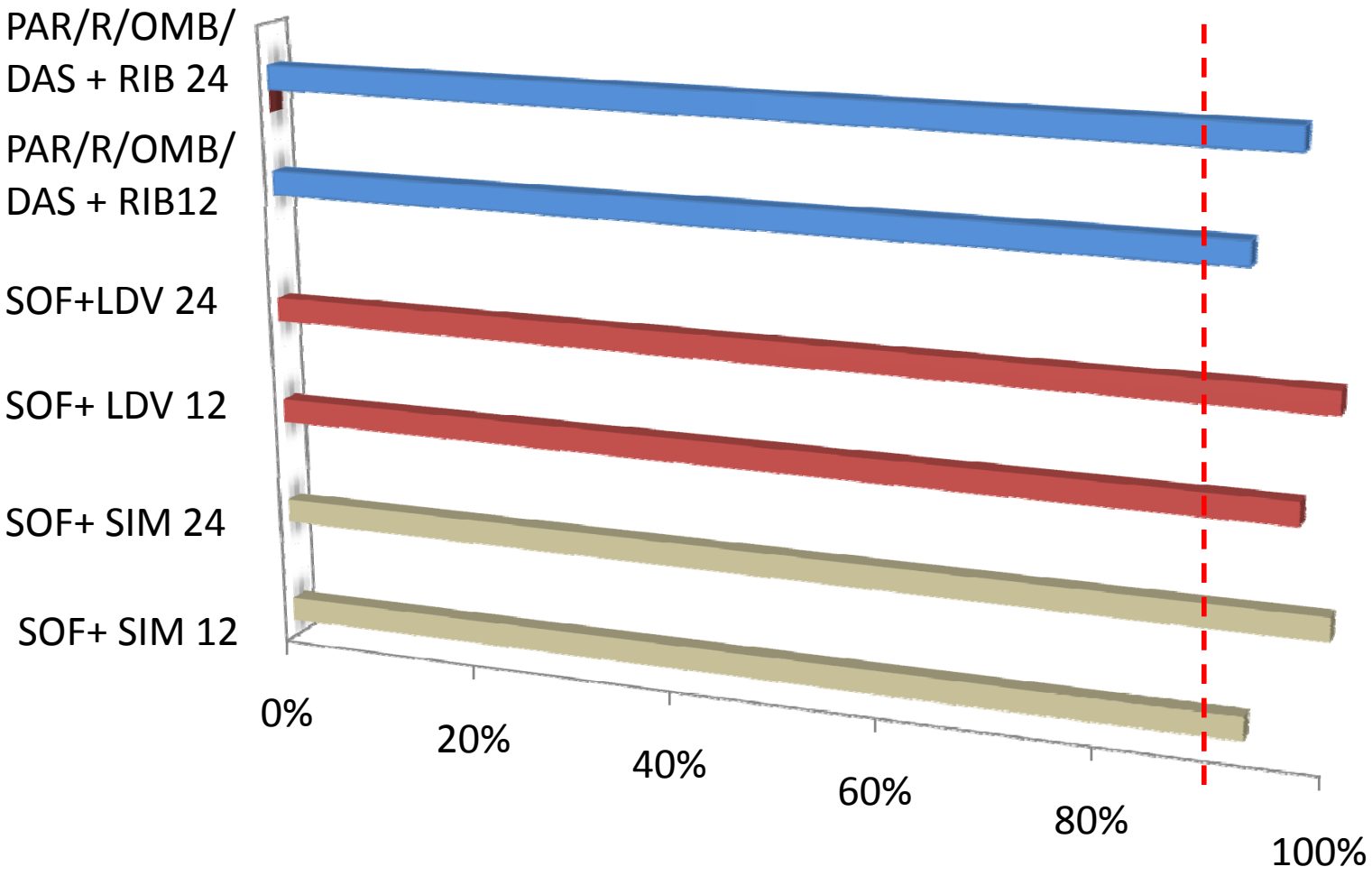
QUEST-II
NCT01455090
NCT 00874770
SAPHIRE
PEARL-III

GENOTIPO 1 previamente tratados



PROMISE
ION-1, ION-2
ELECTRON
COSMOS
NCT01359644C
NCT01497834
SAPHIRE
PEARL-II
TURQUOISE-II

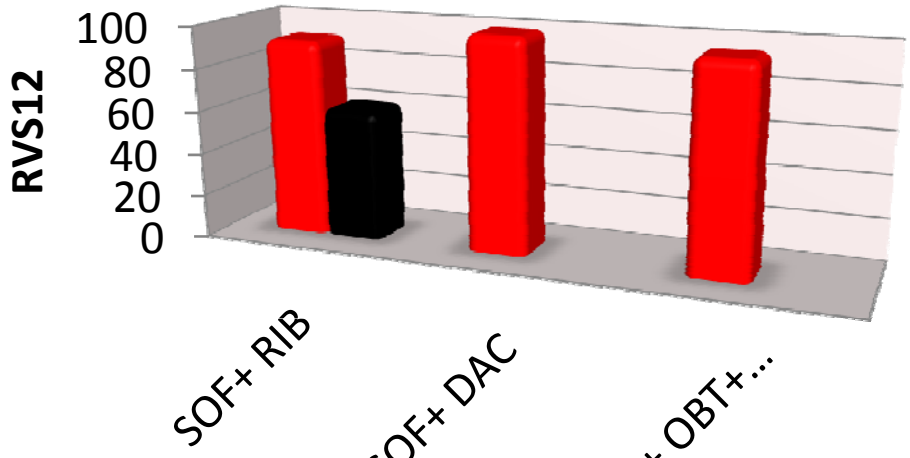
CIRROSIS COMPENSADA GENOTIPO 1 (% SVR)



Poordard,2014, Poordard and Feld 2014, Afdhal 2014 Lawitz 2014

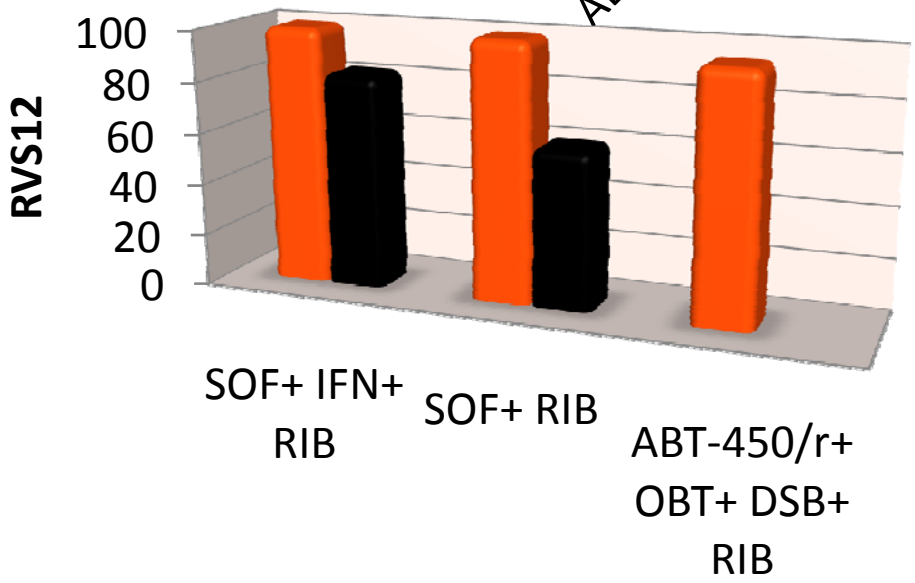
GENOTIPO 2

NAIVE



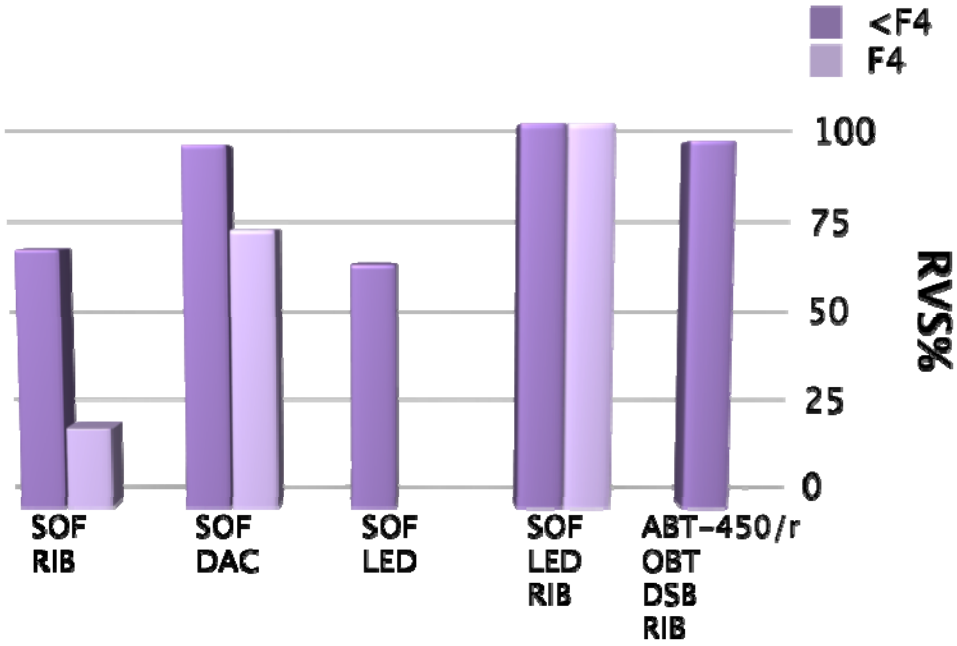
FUSION
POSITRON
NCT01359644C
NTC01464827
NTC01359644

TRATADOS

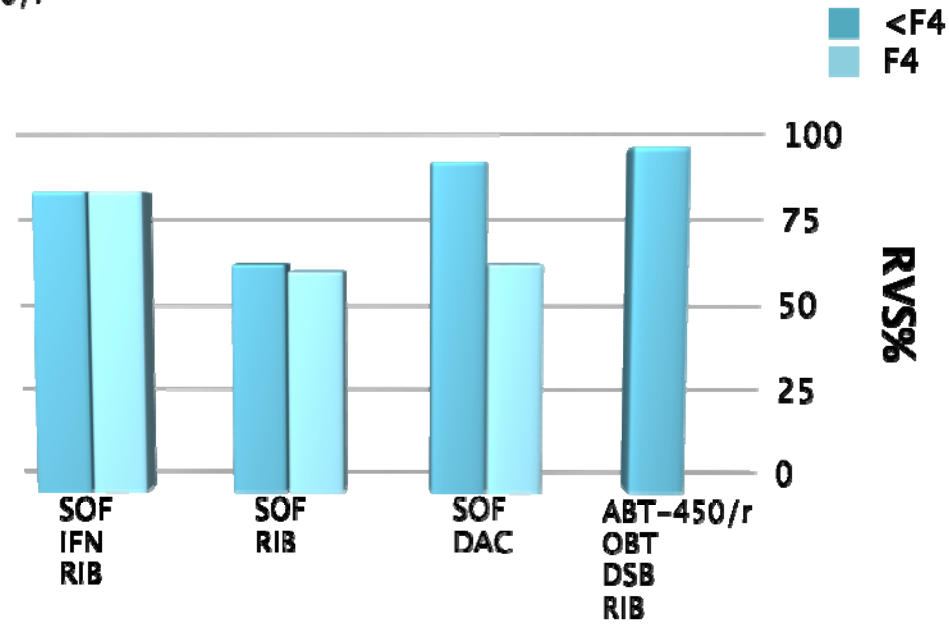


NAIVE

Genotipo 3

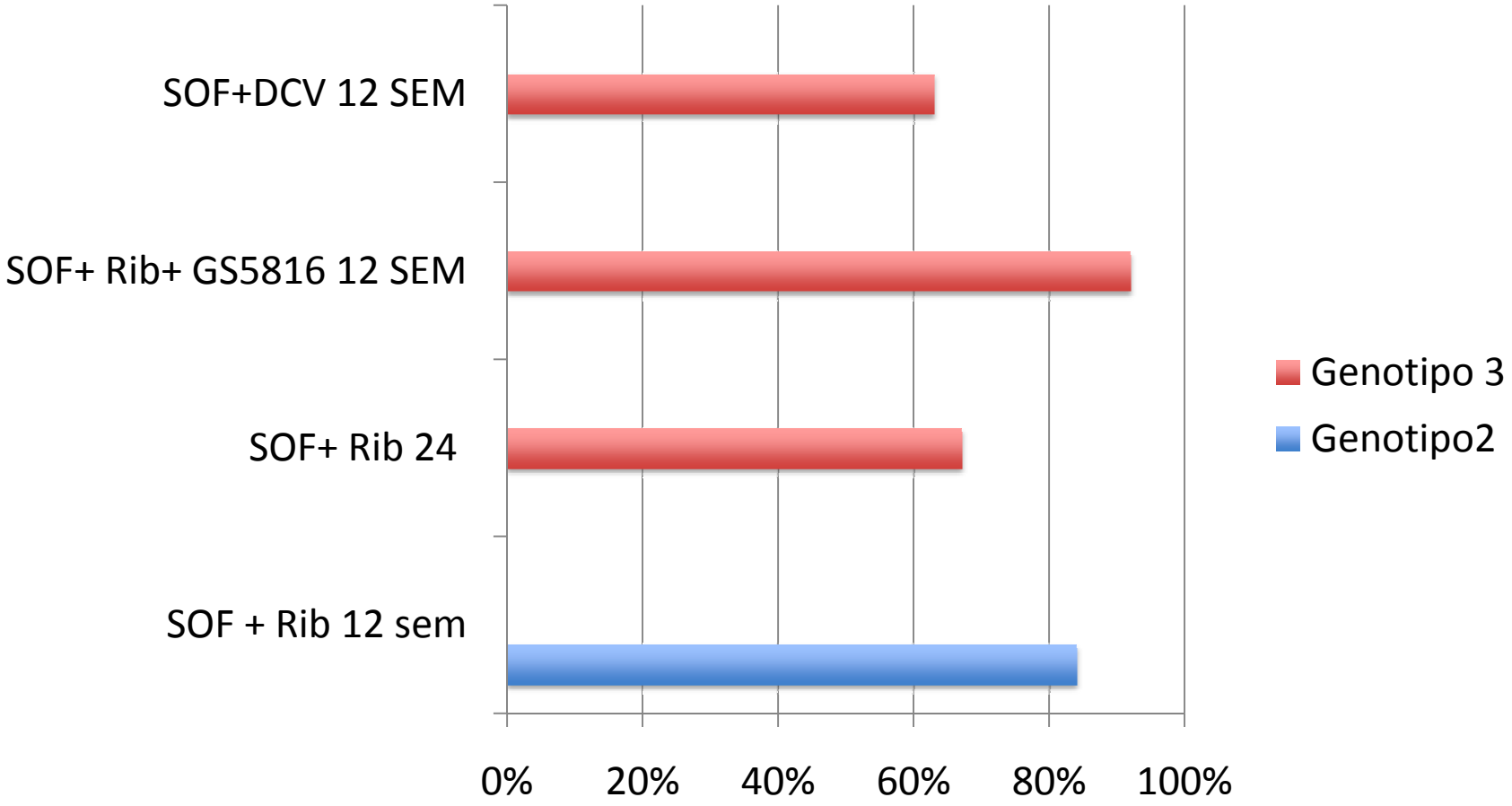


TRATADOS



FUSION
POSITRON
NCT01359644C
NTC01464827
NTC01464827
ALLY-3

Cirrosis Compensada genotipos 2 y 3



Nelson, 2015; Pianco fase 2 2014 comunicado; Zeuzem,2014 Jacobson 2014

Cirroticos:
SOF+RBv 12 w: SVR 63%
SOF+RBv 24 w: SVR 78%
Doss. J Hepatol 2015

Genotipo 4

Tarik J. Hepatol 2015

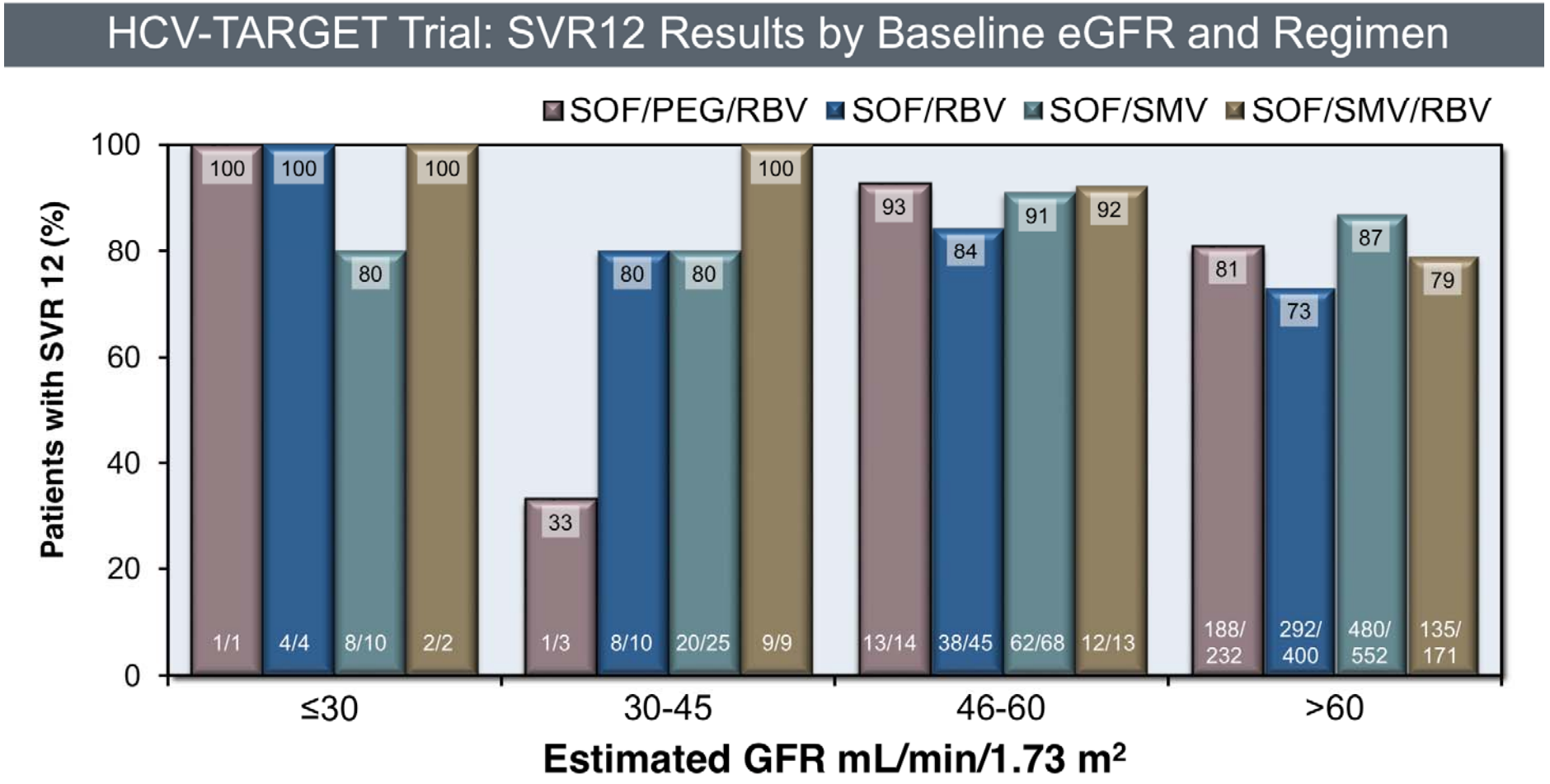
VHC y enfermedad renal

- Perfil de seguridad de DAA y la depuración renal
- Tratamiento de pacientes con insuficiencia renal avanzada y en HD
- Aspectos relacionados con el tratamiento del VHC y el Trasplante renal

Vias principales de aclaramiento de los antivirales. Ajuste de dosis

			(eGFR 15–29 ml/min)	(eGFR <15 ml/min)
Telaprevir	750 mg x3/day	1% renal route	Not required	Not studied
Sofosbuvir	400 mg/day	81% renal route	Not required	Under investigation
3D regimen: ombitasvir	25/150/100 mg once daily	< 2% renal route	Not required	Not recommended
Ledispavir	90 mg daily	< 1% renal route	Not required	Not recommended
	g y		q	g y

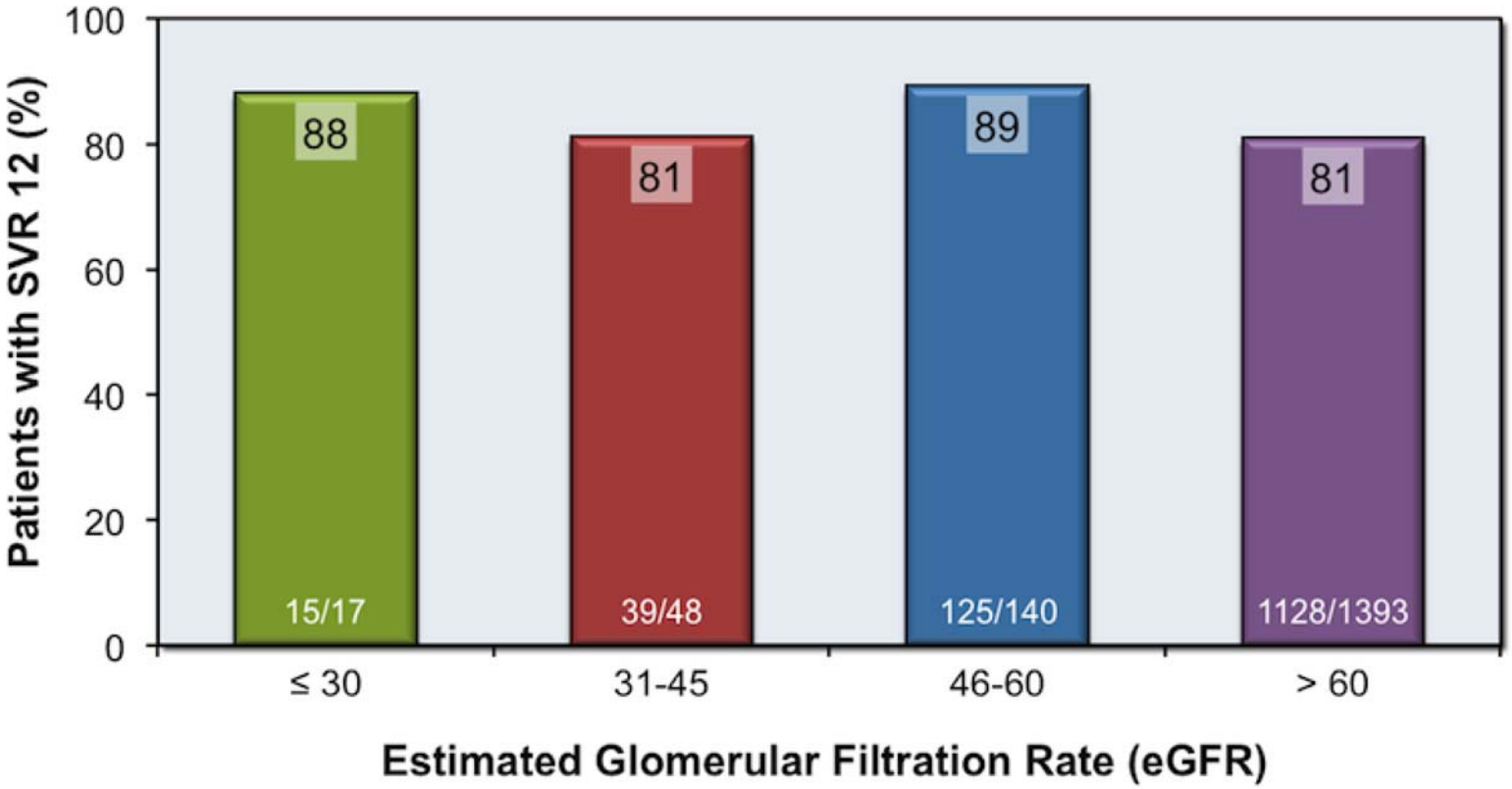
C-TARGET. ESTUDIO OBSERVACIONAL DE PRACTICA CLINICA



N: 19 N: 63 N: 168 N: 1640

Saxena, EASL meeting 2015

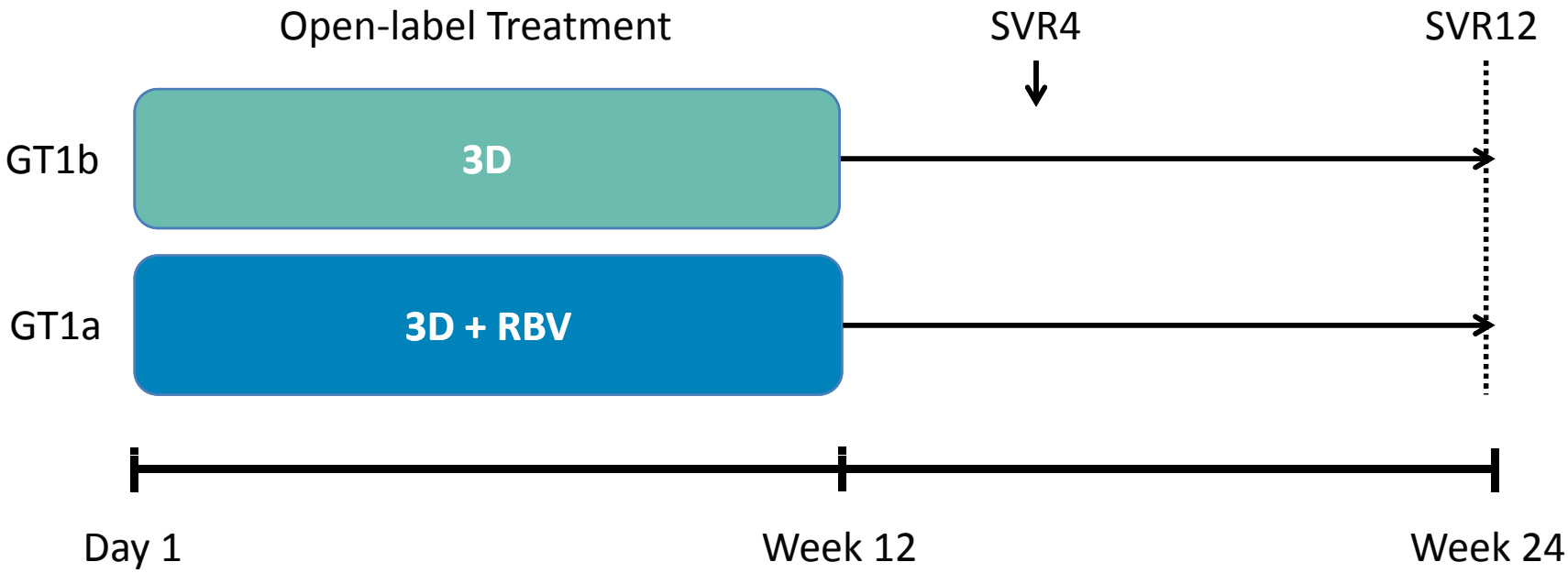
RESPUESTA VIRAL EN FUNCION DE GFR C-TARGET



Saxena, EASL meeting 2015

Multicenter, Open-label, Phase 3b Study: RUBY -1

- 9 sites, all in the United States



- **3D**: Co-formulated OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg BID)
- **For GT1a**: RBV 200 mg QD
- **For GT1b**: No RBV

Pockros, EASL 2015

Baseline Demographics, Clinical Characteristics

	3D±RBV N=20
Male; n (%)	17 (85)
Black; n (%)	14 (70)
Age, years; median (range)	60 (49-69)
Hispanic or Latino ethnicity; n(%)	3 (15)
Degree of fibrosis; n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV viral load, $\log_{10}$ (IU/mL); median (range)	6.6 (5.5-7.6)
GT1a; n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage; n (%)	
4 (eGFR 15-30 mL/min/1.73m^2)	7 (35)
5 (eGFR <15 mL/min/1.73m^2 or requiring dialysis)	13 (65)
On dialysis; n (%)	13 (65)
eGFR, mL/min/1.73m^2; median (range)	10.9 (5.4-29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2-10.8)

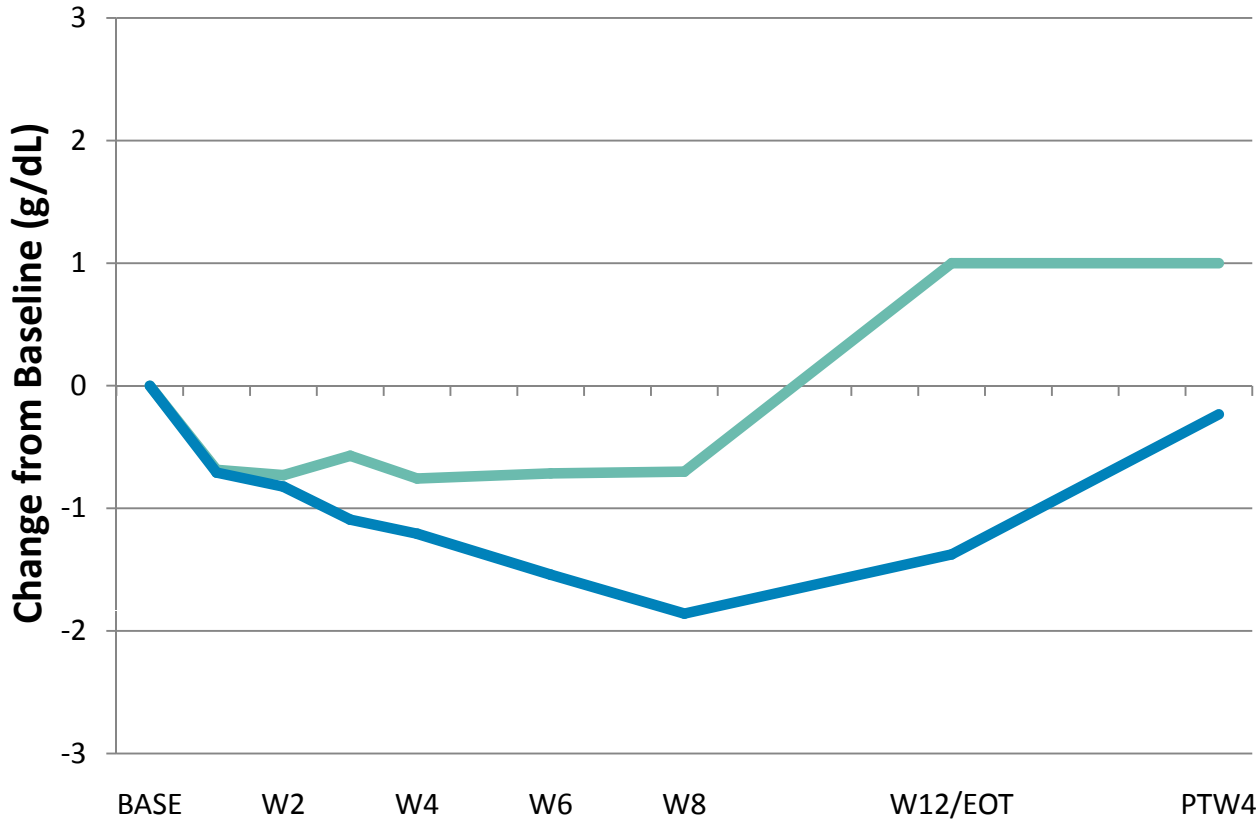
Pockros, EASL 2015

Ribavirin Management

- RBV was started at 200 mg QD for all GT1a-infected patients
- For GT1a patients on hemodialysis, RBV was dosed 4 hours prior to start of hemodialysis
- Hemoglobin was checked weekly for the first month, and at weeks 6, 8, and 12 (end of treatment)
- RBV was interrupted for the following:
  - Hemoglobin decrease of > 2 g/dL in < 4 weeks
  - Hemoglobin value < 10 g/dL

Pockros, EASL 2015

Hematologic Impact of RBV (mean change in Hgb [g/dL])



GT1b: N=	**7**	**7**	**7**	**7**	**7**	**7**	**5**	**2**	**2**
GT1a: N=	**13**	**13**	**13**	**13**	**13**	**12**	**12**	**12**	**9**

8/13 STOP RBV

Pockros, EASL 2015

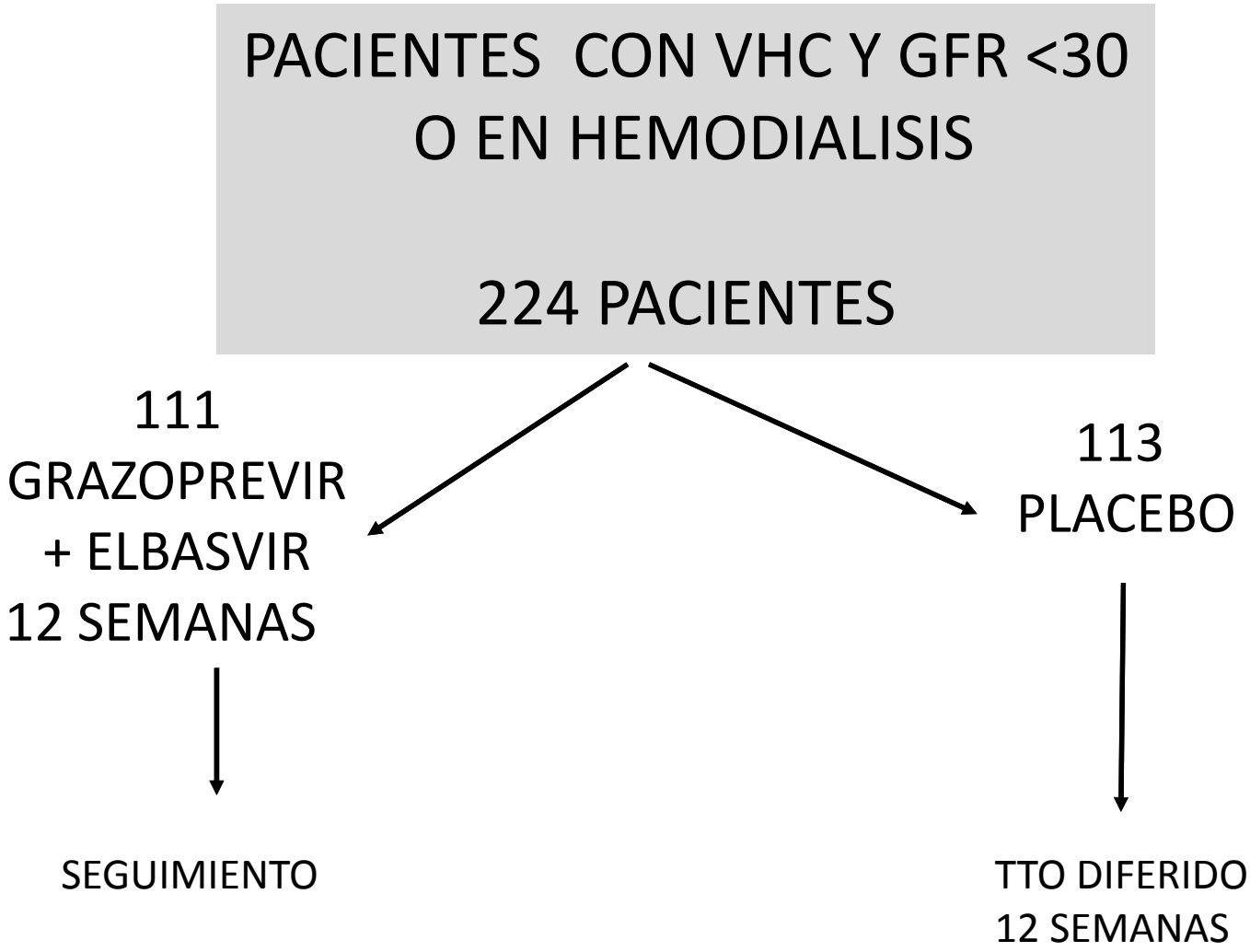
Efficacy

- All patients completing treatment to date had virologic response
- Virologic response has been sustained in all patients who have reached post-treatment weeks 4 and 12 in this ongoing study

Timepoint	N	Virologic Response (n)	Percent
End of Treatment	14	14	100
Post-treatment Week 4	10	10	100
Post-treatment Week 12	2	2	100

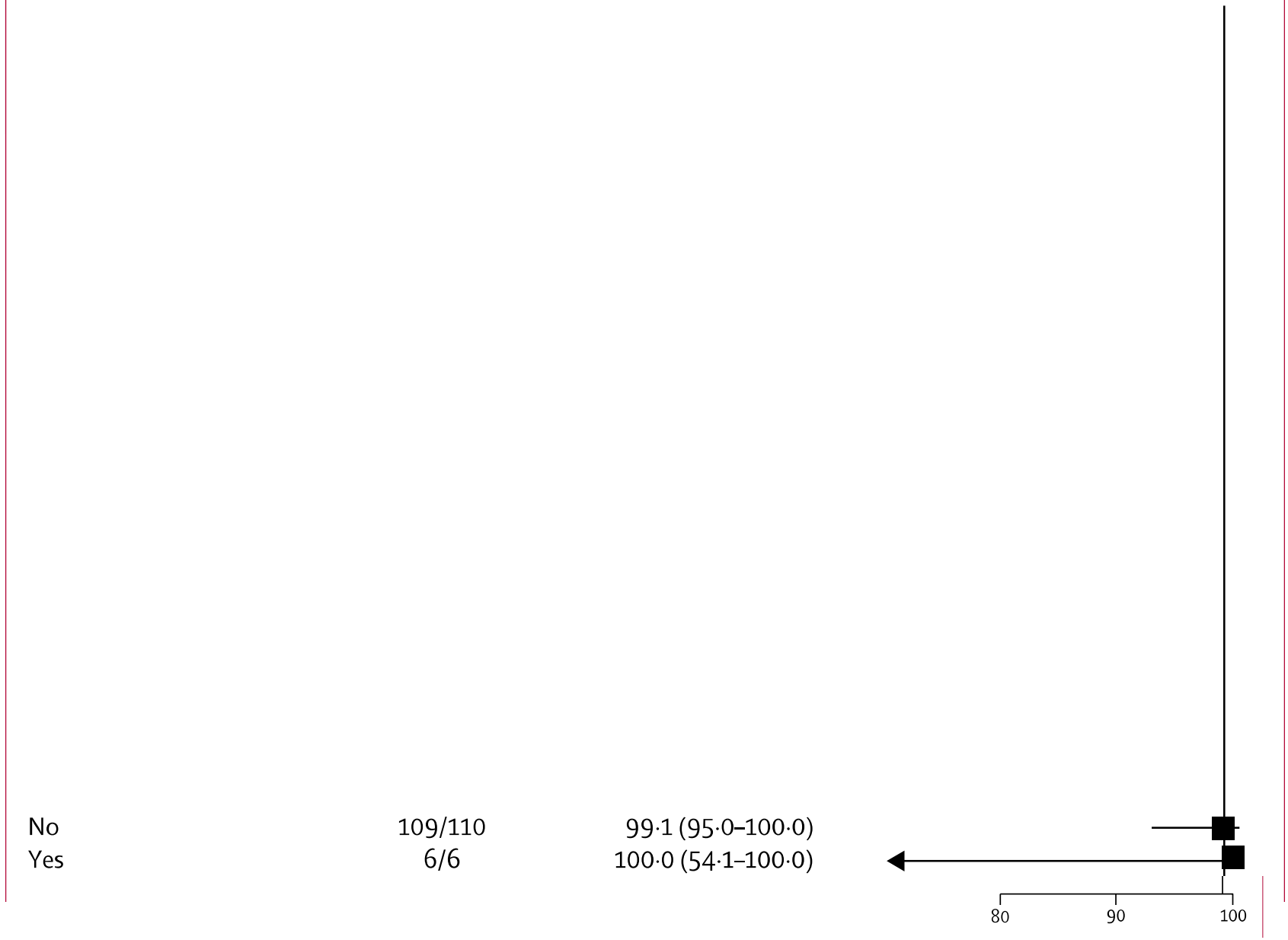
Pockros, EASL 2015

C-SURFER



ROTH D, LANCET . OCT, 6 2015

C- Surfer resultados



C- Surfer cont

CONSIDERACIONES EN TRASPLANTE

	SOF	SOF/LED	SIM	PTV/OMB DSV	DCL
Tacrolimus	NO	NO	NO	RED A 0.5 / SEM	NO
Ciclosporina	NO	NO	SI	RED 20%	NO
Sirolimus/ everolimus	NO	NO	NO	NO DATOS	NO
MMF	NO	NO	NO	RED 50%	NO
Aza	NO	NO	NO	NO	NO

Conclusiones

1.- Los pacientes con insuficiencia renal e infectados por VHC deben de ser tratados con antivirales no solo por la enfermedad hepatica sino por el potencial de reducir la morbimortalidad cardiovascular

2.- Los pacientes con IR deberÍan de recibir una combinacion libre de interferon y si es posible libre también de ribavirina, 12 semanas en pacientes sin cirrosis y 24 semanas en pacientes con cirrosis(B1)

3.- Simeprevir , daclatasvir y la combinacion de paritaprevir-ritonavir ombitasvir y dasabuvir son metabolizados en hígado y pueden ser utilizados en pacientes con Insuficiencia renal severa(A1)

4.- Sofosbuvir no se recomienda para aquellos enfermos con un GFR < de 30 ml/min o con insuficiencia renal avanzada hasta que mas datos apoyen su uso (B2)

5.- En pacientes trasplantados deben de ser tratados con los mismos criterios teniendo en cuenta las interacciones de DAA con Inmunosupresores.