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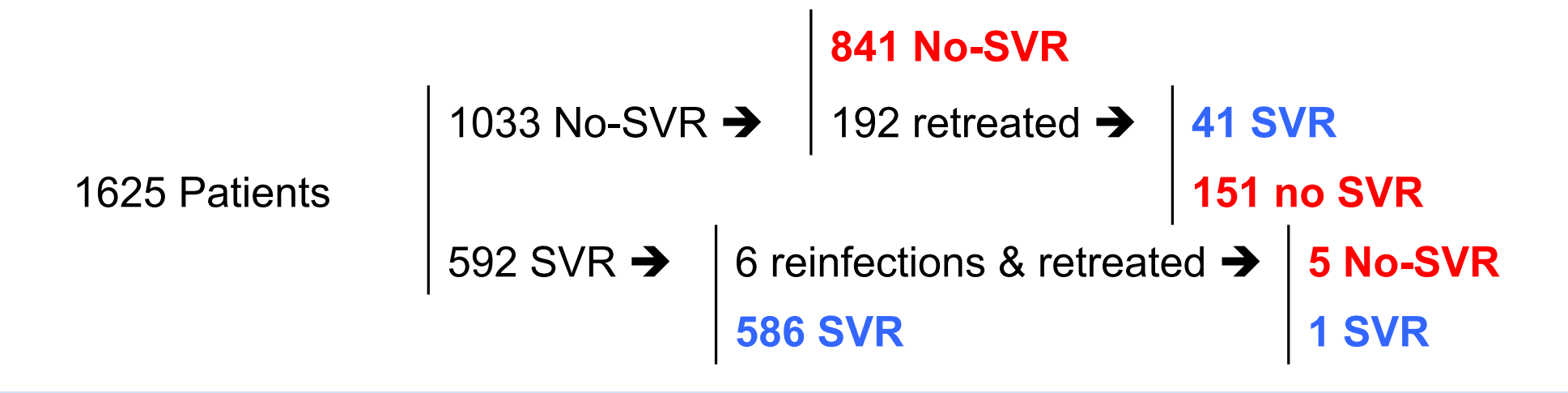
## Background and aims

- We showed that, in HIV/HCV-coinfected patients, a sustained virologic response (SVR) after therapy with interferon plus ribavirin (IF-RB) reduces liver-related complications and mortality<sup>1</sup> as well as HIV progression and mortality not related to liver disease<sup>2</sup>
- Here, we studied the effect of SVR on non-liver-related (NLR) non-AIDS-related (NAR) events and mortality in HIV/HCV-coinfected patients after therapy with IF-RB

<sup>1</sup>Berenguer, J. et al. Hepatology 2009; 50: 407  
<sup>2</sup>Berenguer J, et al. Clinical Infectious Diseases 2012; 55: 728

## Treatment response

- Initial treatment response was categorized as
  - SVR in 592 (36%) patients
    - 6 had a HCV reinfection during follow-up
  - No response in 1033 (64%) patients.
- A total of 198 patients were retreated during follow-up
  - 192 patients who failed the first anti-HCV therapy course
  - 6 patients with reinfections
  - 42 retreated patients achieved SVR (including 1 of 6 reinfected)
- Primary analysis
  - 628 responders (586 + 41 + 1)
  - 997 non-responders (841 + 151 + 5)



## Frequency and rate of events

	Frequency, No. (%)			Rate/100 person-years (95% CI)		
	No SVR N=992	SVR N=633	P <sup>1</sup>	No SVR	SVR	P <sup>2</sup>
Lost to follow-up	162 (16.2)	74 (11.8)	.013	3.19 (2.72 - 3.72)	2.33 (1.83 - 2.92)	.021
Overall mortality	145 (14.5)	30 (4.8)	<.001	2.75 (2.32 - 3.23)	0.93 (0.63 - 1.33)	<.001
Liver-related	83 (8.3)	6 (1.0)	<.001	1.57 (1.25 - 1.95)	0.19 (0.07 - 0.41)	<.001
Non-liver-related	62 (6.2)	24 (3.8)	.036	1.17 (0.90 - 1.50)	0.75 (0.48 - 1.11)	.009
AIDS-related	8 (0.8)	2 (0.3)	.224	0.15 (0.07 - 0.30)	0.06 (0.01 - 0.22)	.045
NLR-NAR	54 (5.4)	22 (3.5)	.075	1.02 (0.77 - 1.33)	0.68 (0.43 - 1.03)	.039
CDC category C disease	43 (4.3)	9 (1.4)	.001	0.81 (0.59 - 1.10)	0.28 (0.13 - 0.53)	.001
Liver decompensation	123 (12.3)	7 (1.1)	<.001	2.44 (2.03 - 2.91)	0.22 (0.09 - 0.45)	<.001
Hepatocellular carcinoma	29 (2.9)	3 (0.5)	.001	0.55 (0.37 - 0.79)	0.09 (0.02 - 0.27)	<.001
Liver transplantation, No. (%)	16 (1.6)	1 (0.2)	.005	0.30 (0.17 - 0.49)	0.03 (0 - 0.17)	.002
NLR-NAR events						
Diabetes mellitus	76 (7.6)	23 (3.7)	.001	1.48 (1.16 - 1.85)	0.72 (0.46 - 1.08)	.004
NLR-NAR cancer	67 (6.7)	33 (5.3)	.231	1.28 (0.99 - 1.63)	1.04 (0.72 - 1.46)	.382
Cardiovascular events	52 (5.2)	39 (6.2)	.396	0.99 (0.74 - 1.30)	1.24 (0.88 - 1.69)	.502
Sepsis requiring hospitalization	62 (6.2)	19 (3.0)	.004	1.19 (0.91 - 1.52)	0.59 (0.36 - 0.93)	.017
Bone events	33 (3.3)	24 (3.8)	.585	0.63 (0.44 - 0.89)	0.75 (0.48 - 1.12)	.422
Renal events	28 (2.8)	6 (1.0)	.011	0.53 (0.35 - 0.77)	0.19 (0.07 - 0.41)	.006

P<sup>1</sup>: Pearson chi-square test; P<sup>2</sup>: Gray's test for cumulative incidence

## Hazard ratio of events during FU Responders vs Non-responders

	Univariate analysis <sup>a</sup>		Multivariate analysis <sup>a,b</sup>	
	HR (95% CI)	P	HR (95% CI)	P
Overall deaths	0.35 (0.24 - 0.52)	<.001	0.37 (0.25 - 0.56)	<.001
	sHR (95% CI)		sHR (95% CI)	
<b>Cause-specific deaths</b>				
Liver-related deaths	0.12 (0.05 - 0.28)	<.001	0.13 (0.06 - 0.30)	<.001
Non-liver-related deaths	0.69 (0.43 - 1.1)	.119	0.73 (0.45 - 1.21)	.225
AIDS-related deaths	0.45 (0.09 - 2.22)	.325	0.36 (0.09 - 1.41)	.143
NLR-NAR deaths	0.73 (0.44 - 1.19)	.204	0.80 (0.47 - 1.36)	.406
<b>New AIDS-defining events</b>	0.34 (0.16 - 0.72)	.004	0.37 (0.17 - 0.80)	.011
<b>Liver-related events</b>				
Liver decompensation	0.09 (0.04 - 0.2)	<.001	0.10 (0.05 - 0.22)	<.001
Hepatocarcinoma	0.12 (0.03 - 0.5)	.004	0.13 (0.03 - 0.50)	.003
Liver transplantation	0.10 (0.01 - 0.77)	.027	0.12 (0.02 - 0.79)	.027
<b>NLR-NAR events</b>				
Diabetes mellitus	0.53 (0.33 - 0.84)	.007	0.56 (0.34 - 0.90)	.018
Cancer	0.91 (0.6 - 1.38)	.650	0.90 (0.57 - 1.43)	.665
Cardiovascular event	1.41 (0.93 - 2.13)	.105	1.56 (1 - 2.43)	.052
Sepsis requiring hospitalization	0.55 (0.33 - 0.92)	.024	0.90 (0.57 - 1.43)	.665
Bone event	1.39 (0.82 - 2.35)	.225	1.27 (0.69 - 2.33)	.442
Renal event	0.39 (0.16 - 0.95)	.038	0.38 (0.15 - 0.98)	.046

<sup>a</sup>Cox regression for comparison of the HR of overall death. Fine and Gray regression for comparison of the sHR of events, in the presence of competing risks.  
<sup>b</sup>Adjusted for age, sex, prior AIDS-defining conditions (yes vs. no), HIV-transmission category (injection drug users vs. non-injection drug users), nadir CD4+ cell count, cART (yes vs. no), undetectable HIV-RNA at baseline (yes vs. no), FIB-4 ≥3.25 (yes vs. no), genotype (3 vs. other genotypes). **Abbreviations:** HR, hazard ratio; CI, confidence interval; sHR, subhazard ratio.

## Design and definitions

<b>Design (GeSIDA 3603)</b>	<ul style="list-style-type: none"> <li>Cohort of HIV/HCV-coinfected patients treated with IF-RB during 2000-2008 in 19 centers (prospective since 2003)</li> <li>Database was modified (June 2014) to include NLR-NAR events</li> </ul>
<b>Events</b>	<ul style="list-style-type: none"> <li>Mortality (overall and cause-specific)</li> <li>Events (liver-related, AIDS-related, NLR-NAR)</li> </ul>
<b>NLR-NAR Events*</b>	<ul style="list-style-type: none"> <li>Cardiovascular events (coronary, cerebrovascular, etc.)</li> <li>Renal (chronic renal failure, dialysis, transplantation)</li> <li>Bone (fractures and avascular bone necrosis)</li> <li>Diabetes mellitus</li> <li>Cancer (NLR-NAR)</li> <li>Sepsis requiring hospitalization (NAR)</li> </ul>
<b>Duration</b>	<ul style="list-style-type: none"> <li>From the date IF-RB was stopped to death or last follow-up visit</li> <li>Administrative censoring date: 31 May, 2014</li> </ul>
<b>Monitoring</b>	<ul style="list-style-type: none"> <li>All centers were monitored before the final analysis</li> </ul>
<b>Analysis</b>	<ul style="list-style-type: none"> <li>As some patients experienced reinfections and some underwent retreatment, we performed several analyses.</li> <li>Primary analysis, patients with SVR after retreatment (after failure or relapse) were included in the SVR group.</li> <li>Sensitivity analyses (x3): i) censoring follow-up in retreated patients at the date of initiation of retreatment, ii) excluding retreated patients, and iii) considering response status as time-dependent</li> </ul>

\*Defined according to the Cohort of the Spanish AIDS Research Network (AIDS 2013; 27:181).

## Patient characteristics

Characteristic	No SVR (n=997)	SVR (n=628)	Total (n=1625)
Male sex, No. (%)	753 (75.5)	466 (74.2)	1219 (75)
Age, y, median (IQR) (baseline)	40 (37 - 43)	40 (37 - 43)	40 (37 - 43)
Follow-up months, median (IQR)	65 (42 - 85)	65 (43 - 86)	65 (43 - 85)
Prior injection drug use, No. (%)	802 (80.4)	510 (81.2)	1312 (80.7)
CDC disease category C, No. (%) <sup>a</sup>	245 (24.6)	125 (19.9) *	370 (22.8)
CD4 <sup>+</sup> nadir, cells/mm <sup>3</sup> , median (IQR)	200 (100 - 313)	212 (113 - 333)	204 (106 - 322)
cART during anti-HCV treatment, No. (%)	848 (85.1)	518 (82.5)	1366 (84.1)
CD4 <sup>+</sup> baseline, cells/mm <sup>3</sup> , median (IQR)	515 (374 - 718)	536 (404 - 729)	527 (391 - 724)
Undetectable HIV RNA baseline, No. (%)	667 (66.9)	460 (73.2) *	1127 (69.4)
HCV genotype, No. (%) <sup>b</sup>			
1	581 (58.3)	224 (35.7) *	805 (49.5)
2	13 (1.3)	24 (3.8) *	37 (2.3)
3	214 (21.5)	332 (52.9) *	546 (33.6)
4	170 (17.1)	40 (6.4) *	210 (12.9)
Unknown	10 (1)	5 (0.8)	15 (0.9)
HCV-RNA ≥ 500 000 IU/mL, No. (%)	644 (64.6)	340 (54.1) *	984 (60.6)
FIB-4 score, No. (%)			
< 3.25	671 (67.3)	486 (77.4) *	1157 (71.2)
≥ 3.25	207 (20.8)	71 (11.3) *	278 (17.1)
Unknown	119 (11.9)	71 (11.3)	190 (11.7)
Current alcohol intake > 50 g/d, No. (%)	58 (5.8)	19 (3) *	77 (4.7)

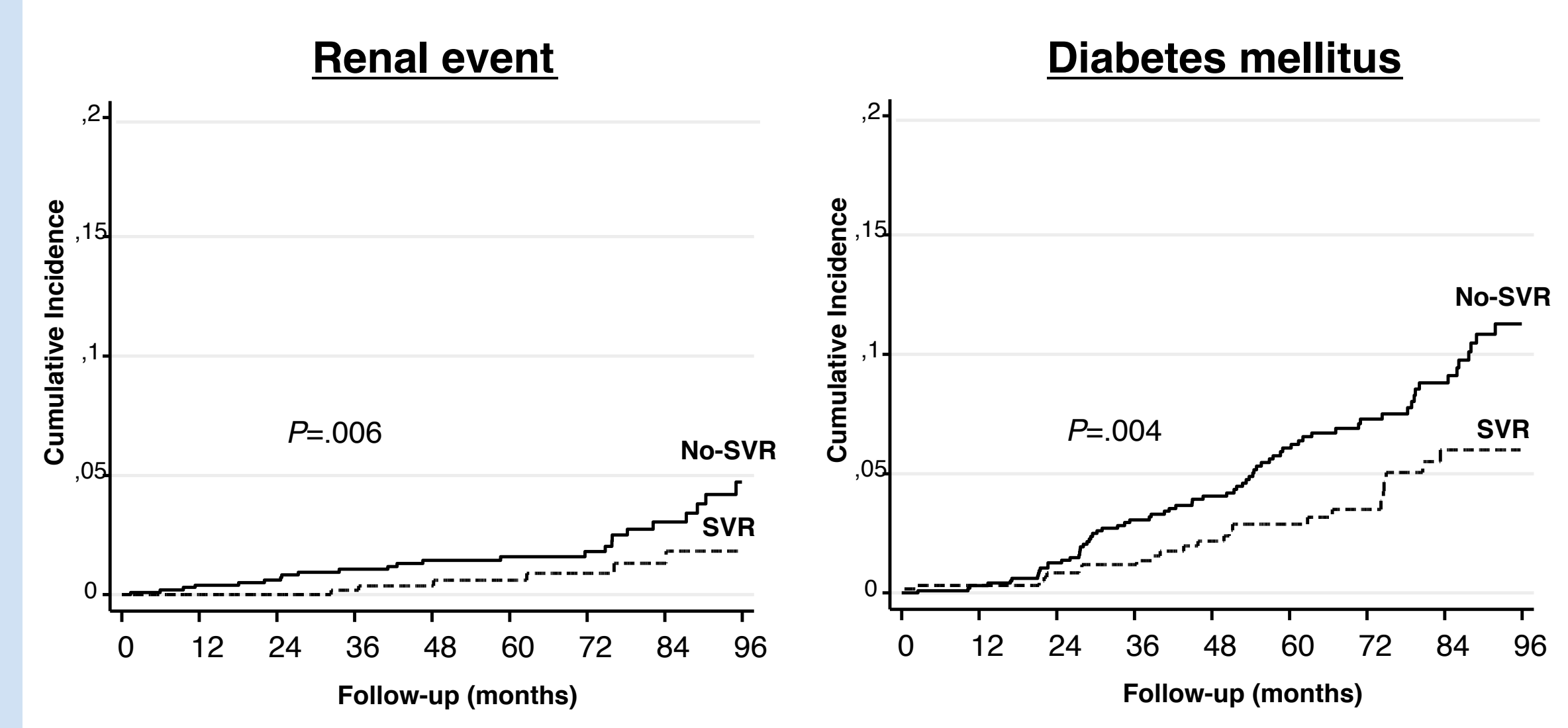
\*P < .05 with the No SVR group.

## Non-AIDS-related events during follow-up

EVENT	No SVR (n=997)	SVR (n=628)	Total (N=1625)	EVENT	No SVR (n=997)	SVR (n=628)	Total (N=1625)
<b>Diabetes mellitus</b> <sup>1</sup>	76 (7.6)	22 (3.5)	98 (6.0)	<b>Cardiovascular events</b>	52 (5.2)	36 (5.7)	88 (5.4)
<b>Cancer (NLR-NAR)</b>	66 (6.6)	31 (4.9)	97 (6.0)	Acute myocardial infarction	19 (1.9)	22 (3.5)	41 (2.5)
Lung	7 (0.7)	5 (0.8)	12 (0.7)	Angina	8 (0.8)	2 (0.3)	10 (0.6)
Anus	6 (0.6)	2 (0.3)	8 (0.5)	Cerebrovascular transient ischemic attack	2 (0.2)	3 (0.5)	5 (0.3)
Head and neck	4 (0.4)	3 (0.5)	7 (0.4)	Cerebrovascular reversible ischemic deficit	2 (0.2)	0 (0)	2 (0.1)
Vagina/vulva	6 (0.6)	1 (0.2)	7 (0.4)	Cerebrovascular established stroke	3 (0.3)	4 (0.6)	7 (0.4)
Colorectal	6 (0.6)	0 (0)	6 (0.4)	Asymptomatic cerebrovascular disease	0 (0)	1 (0.2)	1 (0.1)
Breast	5 (0.5)	0 (0)	5 (0.3)	Peripheral arterial disease	7 (0.7)	2 (0.3)	9 (0.6)
Skin non-melanoma	5 (0.5)	0 (0)	5 (0.3)	Congestive heart failure	4 (0.4)	1 (0.2)	5 (0.3)
Hodgkin lymphoma	2 (0.2)	2 (0.3)	4 (0.2)	Pulmonary hypertension	5 (0.5)	1 (0.2)	6 (0.4)
Brain	3 (0.3)	0 (0)	3 (0.2)	Mesenteric ischemia	1 (0.1)	0 (0)	1 (0.1)
Sarcoma	1 (0.1)	2 (0.3)	3 (0.2)	Aortic dissection	1 (0.1)	0 (0)	1 (0.1)
Penis	2 (0.2)	1 (0.2)	3 (0.2)	<b>NAR sepsis requiring hospitalization</b>	62 (6.2)	18 (2.9)	80 (4.9)
Esophagus	1 (0.1)	1 (0.2)	2 (0.1)	<b>Bone-related events</b>	33 (3.3)	23 (3.7)	56 (3.4)
Stomach	2 (0.2)	0 (0)	2 (0.1)	Large bone fracture	23 (2.3)	18 (2.9)	41 (2.5)
Other hematologic	1 (0.1)	1 (0.2)	2 (0.1)	Avascular necrosis of bone	5 (0.5)	5 (0.8)	10 (0.6)
Prostate	1 (0.1)	1 (0.2)	2 (0.1)	Vertebral fracture	5 (0.5)	0 (0)	5 (0.3)
Other	14 (1.4)	12 (1.9)	26 (1.6)	<b>Renal events</b>	28 (2.8)	6 (1.0)	34 (2.1)
				Chronic kidney disease <sup>2</sup>	25 (2.5)	5 (0.8)	30 (1.8)
				Initiation of dialysis	3 (0.3)	1 (0.2)	4 (0.2)

<sup>1</sup>Fasting plasma glucose >126 mg/dL (7.0 mmol/L) on at least 2 separate consecutive occasions, no evidence of normal glucose levels in the range.  
<sup>2</sup>Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup> for more than 3 months. eGFR can be calculated with CKD-EPI or MDRD formulas.

## Cumulative incidence of renal events and diabetes mellitus



Differences were compared by the Gray's test

## Conclusions

- ① Eradication of HCV in coinfecting patients was independently associated with a reduction in the hazard of overall death and LR death but not of NLR death.
- ② Eradication of HCV in coinfecting patients was also independently associated with a reduction in the hazard of renal events and diabetes mellitus.
- ③ Eradication of HCV was not independently associated with a reduction in the hazard of cancer, bone events, and sepsis requiring hospitalization.
- ④ A non-significant trend was found towards an increased hazard of cardiovascular events in responders in comparison with non-responders.
- ⑤ All findings were confirmed by the 3 sensitivity analyses

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