Effects of Sustained Virological Response on the risk of liver transplant, hepatocellular carcinoma, death and re-infection: meta-analysis of 129 studies in 34,563 patients with Hepatitis C infection.

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What are the clinical benefits of Sustained Virological Response (SVR)?

New Direct Acting Antiviral (DAA) treatments for Hepatitis C can lead to sustained virological response (SVR) in over 90% of treated people.

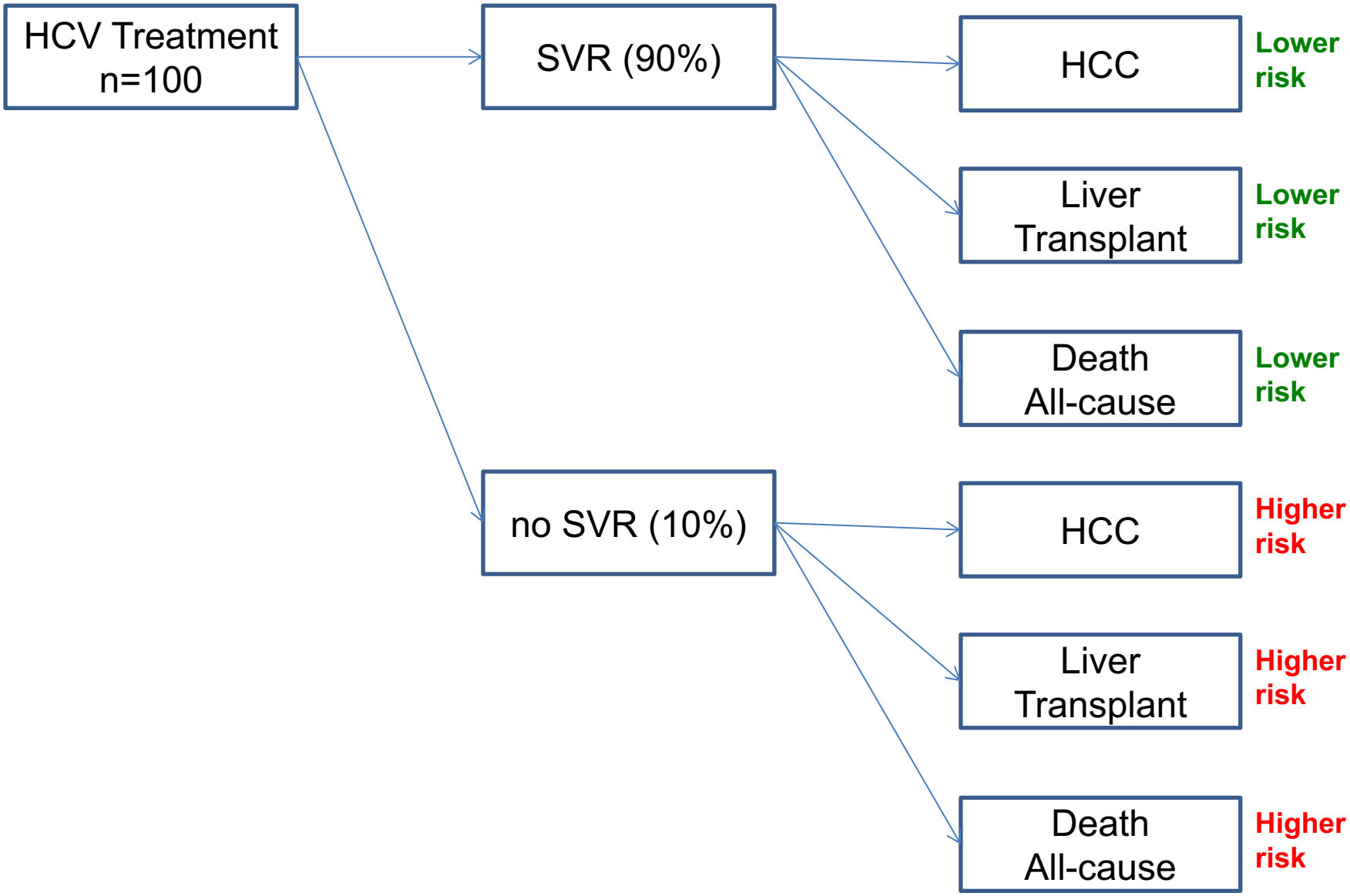
In previous studies of people treated for Hepatitis C, SVR has lowered the risks of:

- Hepatocellular Carcinoma (HCC)
- Liver Transplant
- Liver-related death
- All cause mortality (including other effects of SVR, e.g. insulin resistance)

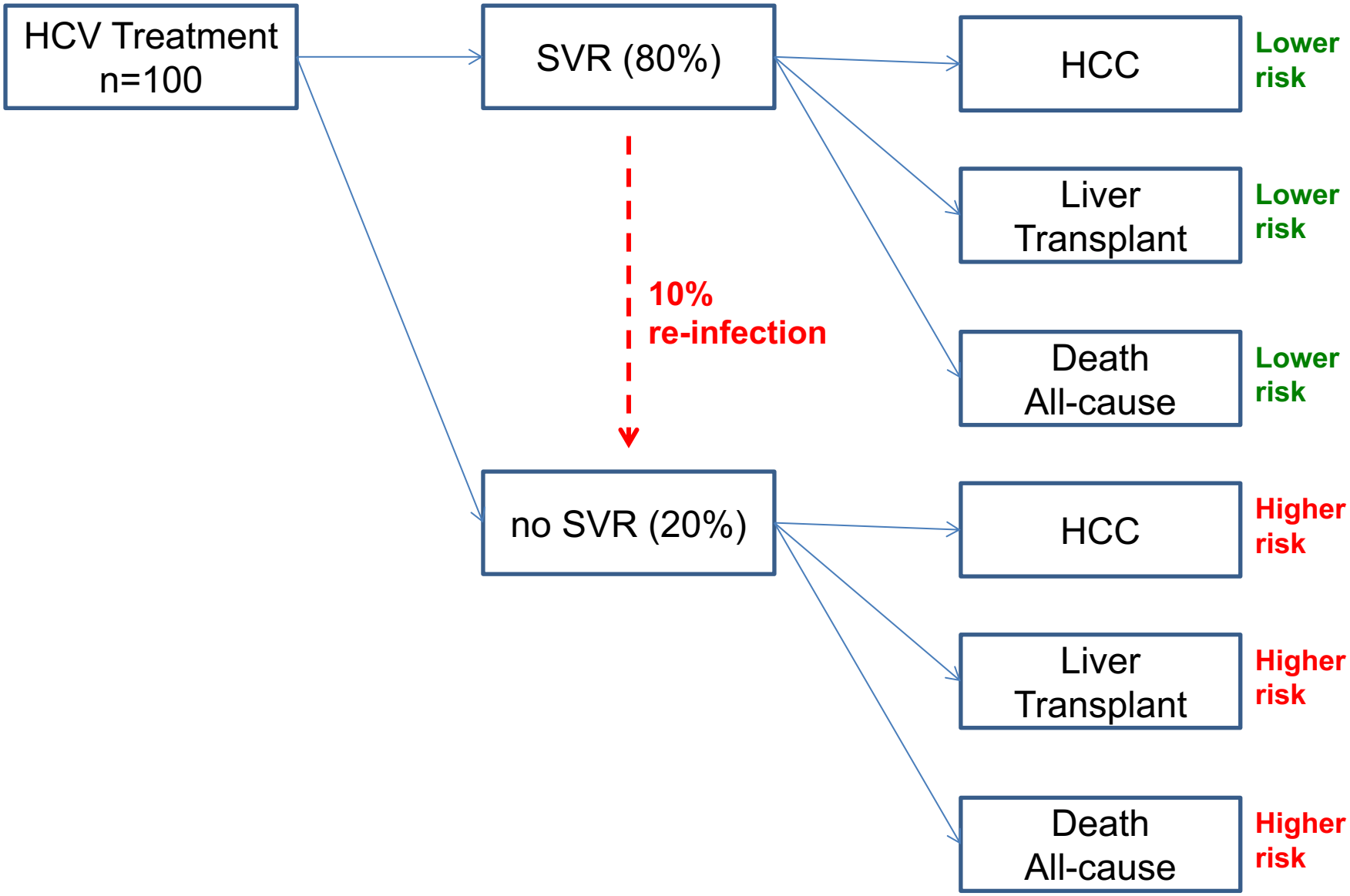
However, these results have not been consistently seen in all studies.

Re-infection post treatment could reverse these benefits

Outcomes post-treatment: SVR, no SVR



Outcomes post-treatment: SVR, no SVR



Analysing effects of SVR on HCC, liver transplant and survival

A MEDLINE/EMBASE searched identified all studies assessing outcomes for people with versus without SVR (typically on pegylated interferon/ribavirin treatment).

We used the combined data to calculate the 5-year risks of Hepatocellular Carcinoma (HCC), liver transplant and all-cause mortality for patients with versus without SVR.

Three groups were analysed:

1. General mono-infected patients
2. Cirrhotic mono-infected patients
3. HIV/HCV co-infected patients

Where available, we compared the results from univariate versus multivariate analyses of these outcomes (to control for baseline confounding).

Analysing rates of HCV re-infection

A second MEDLINE/EMBASE searched identified all studies assessing re-infection with HCV after SVR24 (6 months post-treatment).

Three groups were analysed:

1. Mono-infected: general
2. Mono-infected: IVDU/prisoners
3. HIV/HCV co-infected (all)

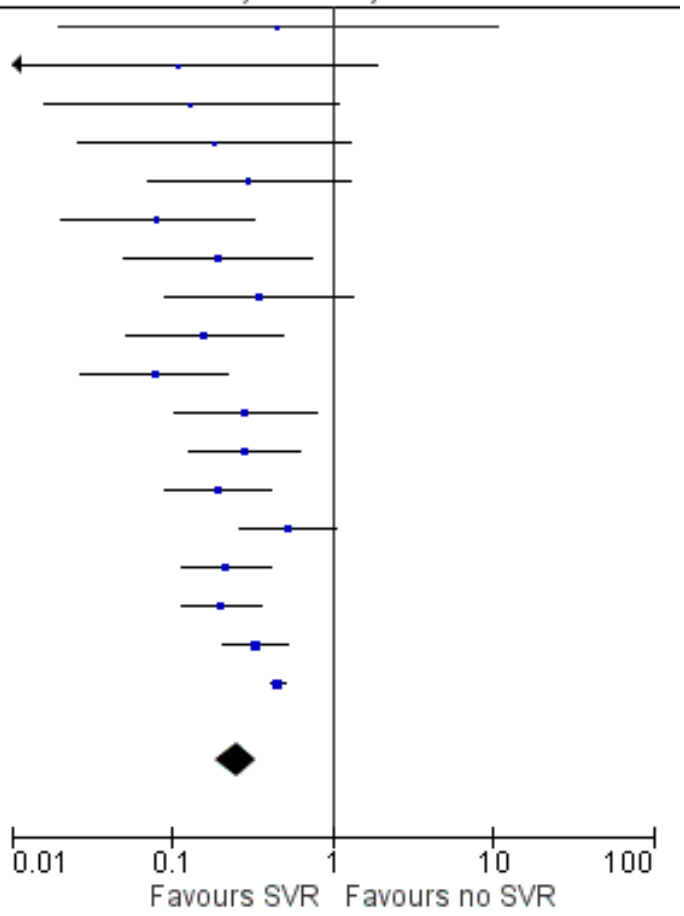
We used the combined data from each group to calculate the 5-year risks of re-infection with HCV, defined as sustained HIV RNA detectability at least 6 months post-treatment, for people with SVR24.

Risk of death (all-cause) for people with SVR vs No SVR, general cohorts. univariate analysis

Study or Subgroup	SVR Events	SVR Total	No SVR Events	No SVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Giannini 2001	0	15	1	21	0.9%	0.46 [0.02, 10.54]
Di Martino V 2011	0	59	9	125	1.1%	0.11 [0.01, 1.87]
Reimer J 2011	1	284	6	224	1.8%	0.13 [0.02, 1.08]
Coverdale 2004	1	50	32	293	2.1%	0.18 [0.03, 1.31]
Tanaka H 2000	2	175	16	419	3.3%	0.30 [0.07, 1.29]
Singal AJ 2013	2	83	40	134	3.6%	0.08 [0.02, 0.33]
Iacobellis A 2011	2	24	22	51	3.7%	0.19 [0.05, 0.76]
Veldt BJ 2004	6	286	3	50	3.7%	0.35 [0.09, 1.35]
Yu ML 2006	4	715	12	342	4.8%	0.16 [0.05, 0.49]
Rutter K 2013	4	331	19	123	5.2%	0.08 [0.03, 0.23]
Imazeki F 2013	4	116	29	239	5.4%	0.28 [0.10, 0.79]
Yoshida H 2002	7	817	49	1613	7.2%	0.28 [0.13, 0.62]
Kasahara A 2004	7	738	94	1930	7.4%	0.19 [0.09, 0.42]
Arase Y 2007	9	140	44	360	8.1%	0.53 [0.26, 1.05]
Maruoka D 2012	10	221	74	356	8.6%	0.22 [0.11, 0.41]
Innes HA 2011	13	560	75	655	9.2%	0.20 [0.11, 0.36]
Dieperink E 2014	19	222	81	314	10.4%	0.33 [0.21, 0.53]
Backus 2011	409	7434	1126	9430	13.5%	0.46 [0.41, 0.51]
Total (95% CI)		**12270**		**16679**	**100.0%**	**0.25 [0.18, 0.34]**
Total events	500		1732			

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 42.20$, df = 17 (P = 0.0006); $I^2 = 60\%$

Test for overall effect: Z = 8.86 (P < 0.00001)

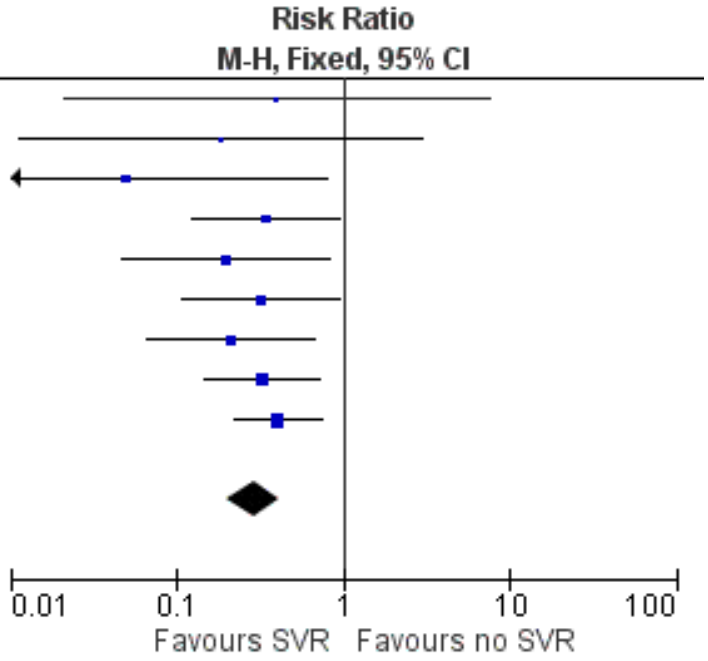


Risk of death (all cause) for people with SVR vs No SVR: Cirrhosis cohorts: univariate analysis

Study or Subgroup	SVR Events	SVR Total	No SVR Events	No SVR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kumar R 2005	0	8	2	17	1.1%	0.40 [0.02, 7.48]
Iacobellis A 2007	0	13	9	48	2.8%	0.18 [0.01, 2.97]
Braks RE 2007	0	37	20	76	9.0%	0.05 [0.00, 0.80]
Mallet 2008	4	39	17	57	9.1%	0.34 [0.13, 0.94]
Veldt 2007	2	142	24	337	9.4%	0.20 [0.05, 0.83]
Van der Meer AJ 2012	3	33	61	215	10.8%	0.32 [0.11, 0.96]
Morgan TR 2010	3	140	39	386	13.8%	0.21 [0.07, 0.68]
Bruno S 2007	6	124	114	769	21.0%	0.33 [0.15, 0.73]
Aleman S 2013	11	110	48	193	23.1%	0.40 [0.22, 0.74]
Total (95% CI)		**646**		**2098**	**100.0%**	**0.29 [0.20, 0.42]**
Total events	29		334			

Heterogeneity: $Chi^2 = 3.60$, $df = 8$ ($P = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 6.70$ ($P < 0.00001$)

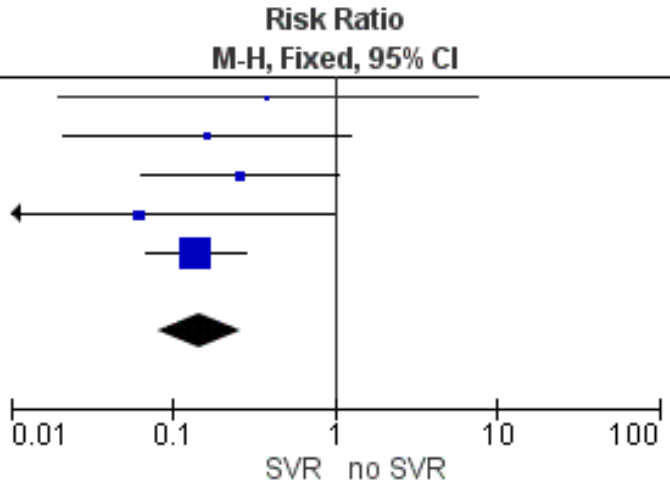


Risk of death (all cause) for SVR vs non-SVR: HIV/HCV Co-infected: univariate analysis

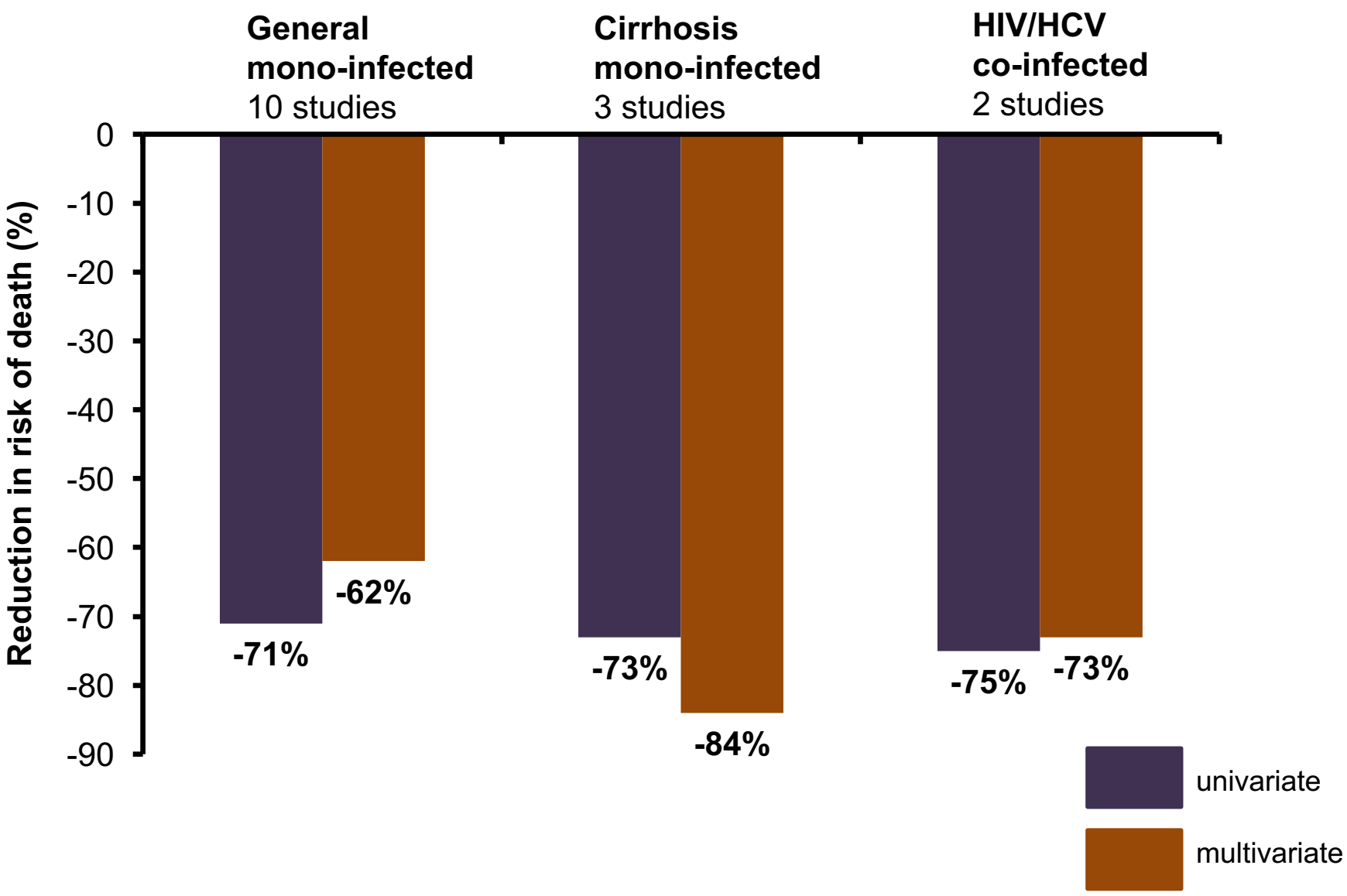
Study or Subgroup	SVR Events	SVR Total	No SVR Events	No SVR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Peribanez-Gonzalez M 2013	0	14	2	28	1.6%	0.39 [0.02, 7.55]
Labarga P 2014	1	138	9	201	7.0%	0.16 [0.02, 1.26]
Mira JA 2013	2	43	22	123	10.9%	0.26 [0.06, 1.06]
Limketkai 2012	0	36	38	176	12.8%	0.06 [0.00, 0.99]
Berenguer J 2012	8	626	90	973	67.6%	0.14 [0.07, 0.28]
Total (95% CI)		**857**		**1501**	**100.0%**	**0.15 [0.08, 0.26]**
Total events	11		161			

Heterogeneity: Chi² = 1.44, df = 4 (P = 0.84); I² = 0%

Test for overall effect: Z = 6.41 (P < 0.00001)



Risk of death (all cause) for SVR vs non-SVR: comparing univariate and multivariate analyses

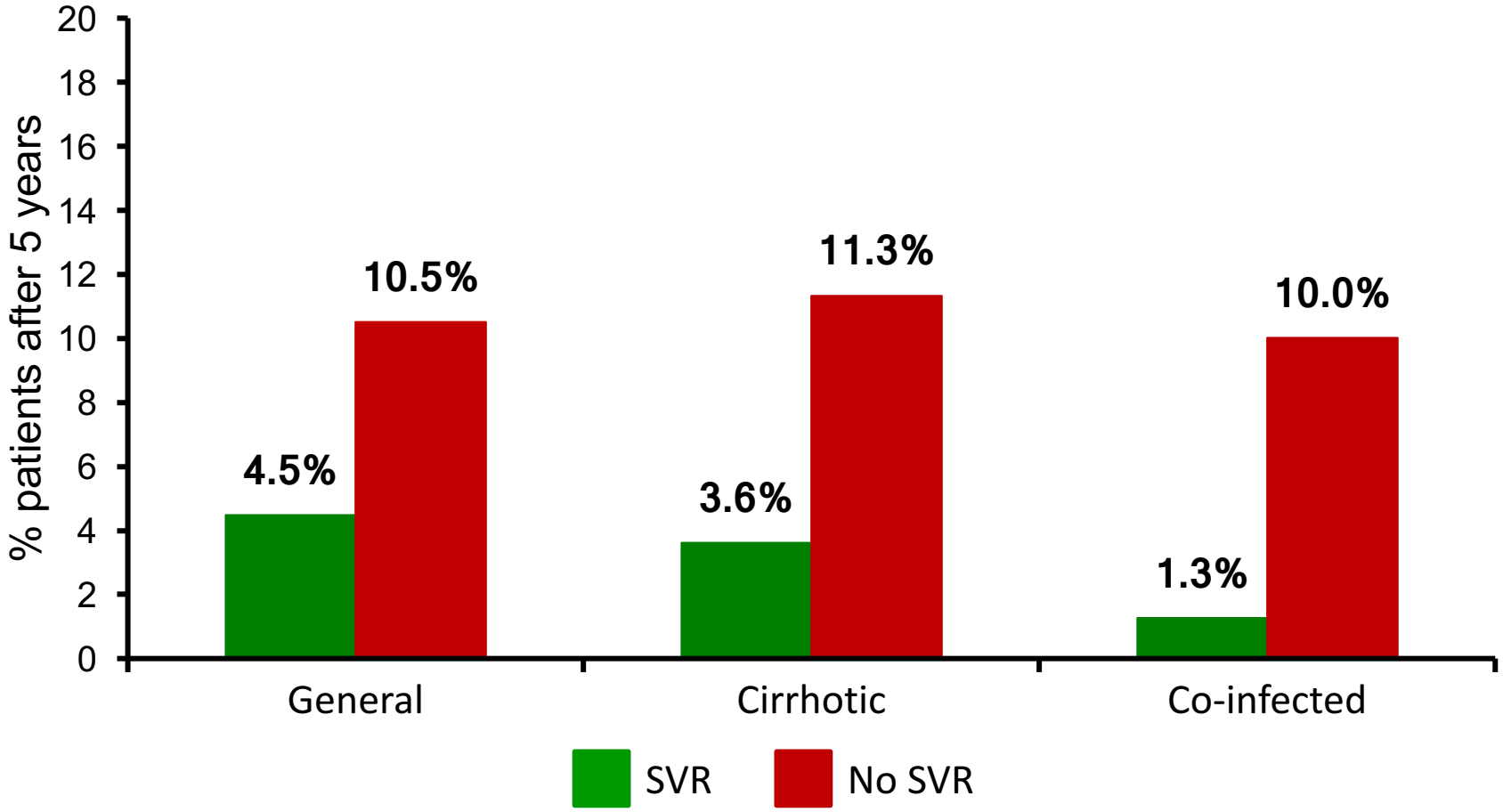


Five year outcomes: deaths (all-cause)

General: 18 studies
n=29,269
Avg. FU=4.6 years

Cirrhotic: 9 studies
n=2,734
Avg. FU=6.6 years

HIV/HCV: 5 studies
n=2,560
Avg. FU=5.1 years

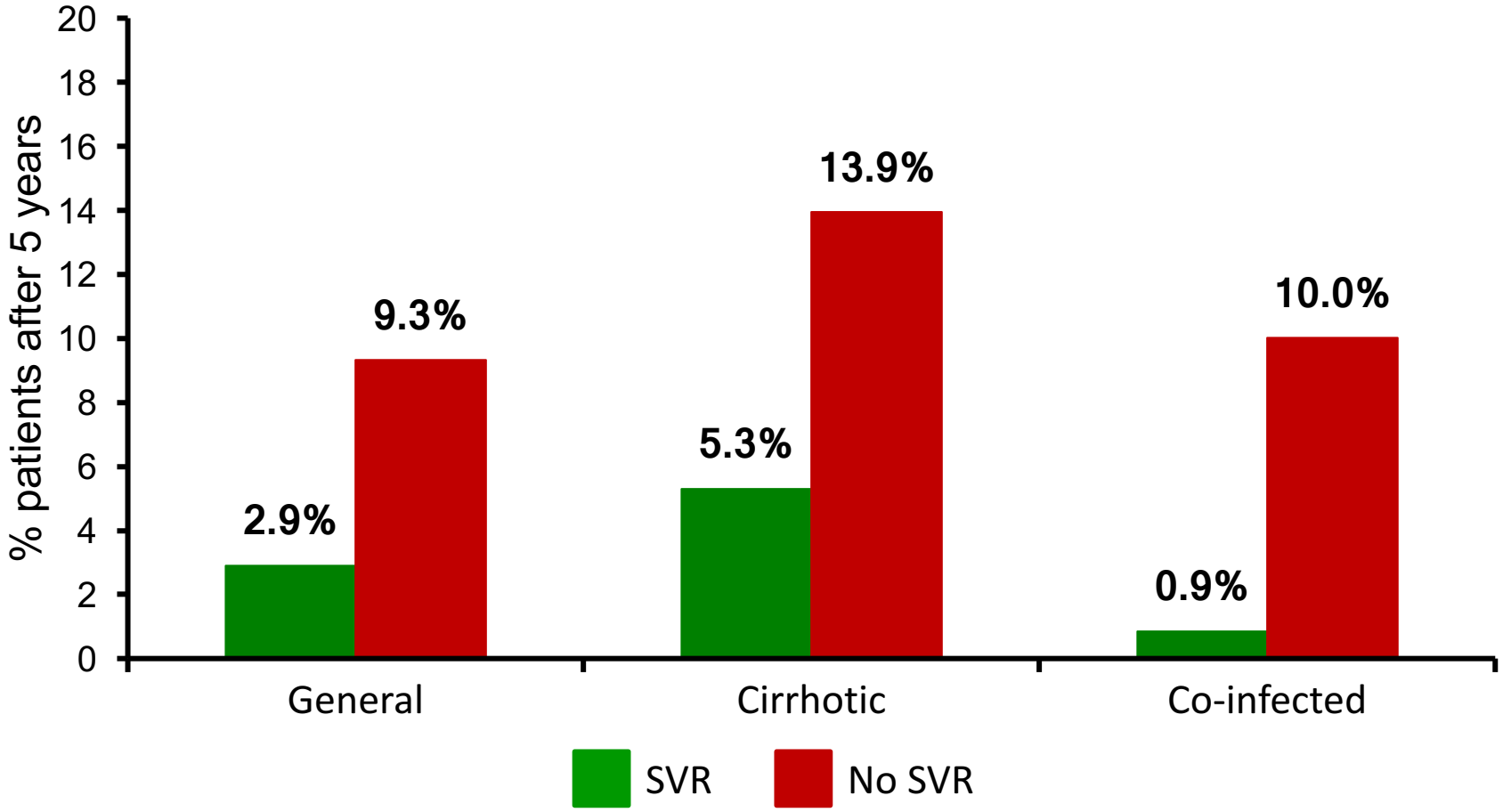


Five year outcomes: Hepatocellular carcinoma (HCC)

General: 21 studies
n=12,496
Avg. FU=6.1 years

Cirrhotic: 18 studies
n=4,987
Avg. FU=6.6 years

HIV/HCV: 3 studies
n=2,085
Avg. FU=4.7 years

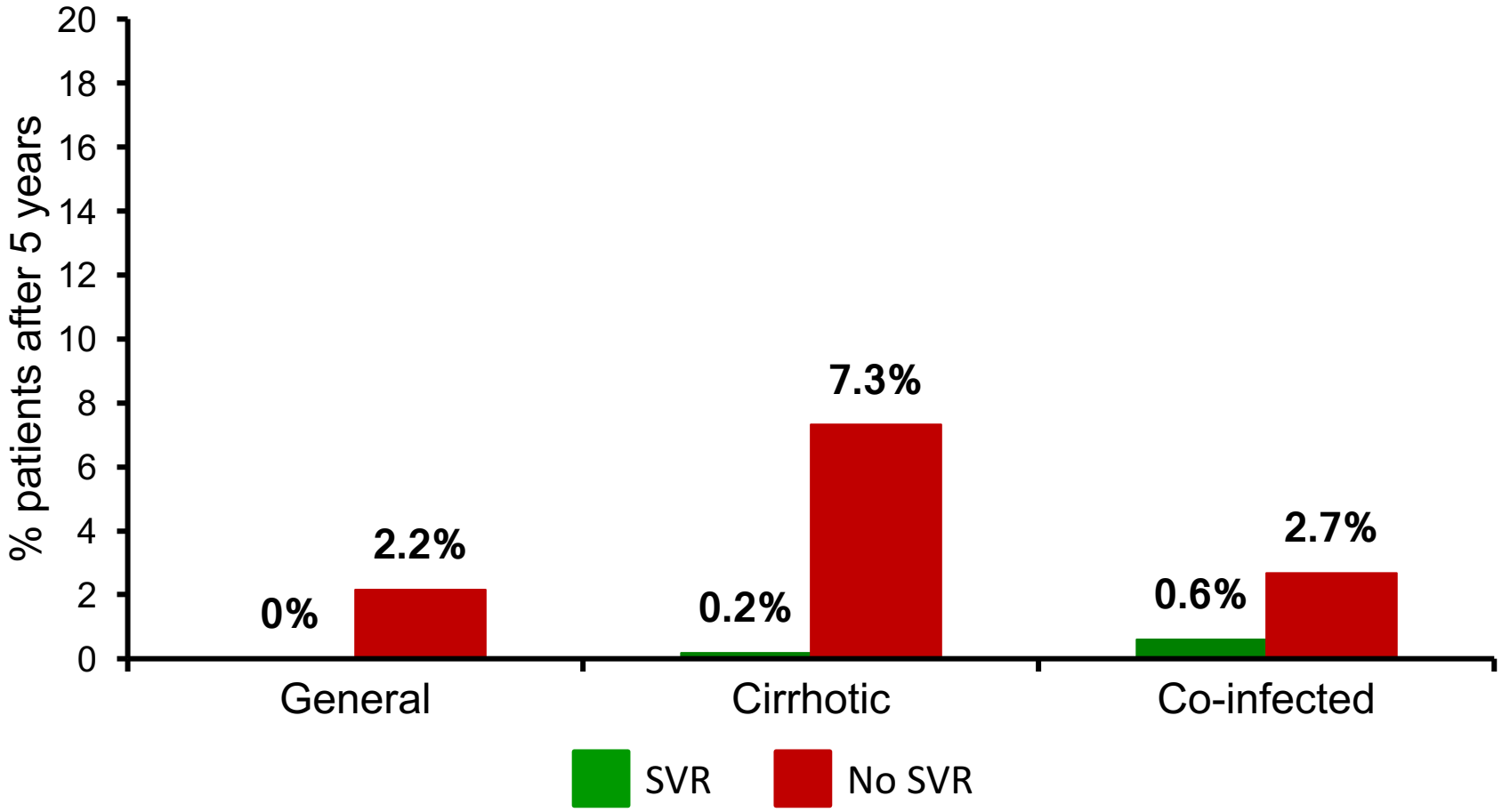


Liver transplantation after 5 years

General: 1 study
n=108
Avg. FU=4.2 years

Cirrhotic: 2 studies
n=1,046
Avg. FU=7.7 years

HIV/HCV: 2 studies
n=2,039
Avg. FU=4.9 years

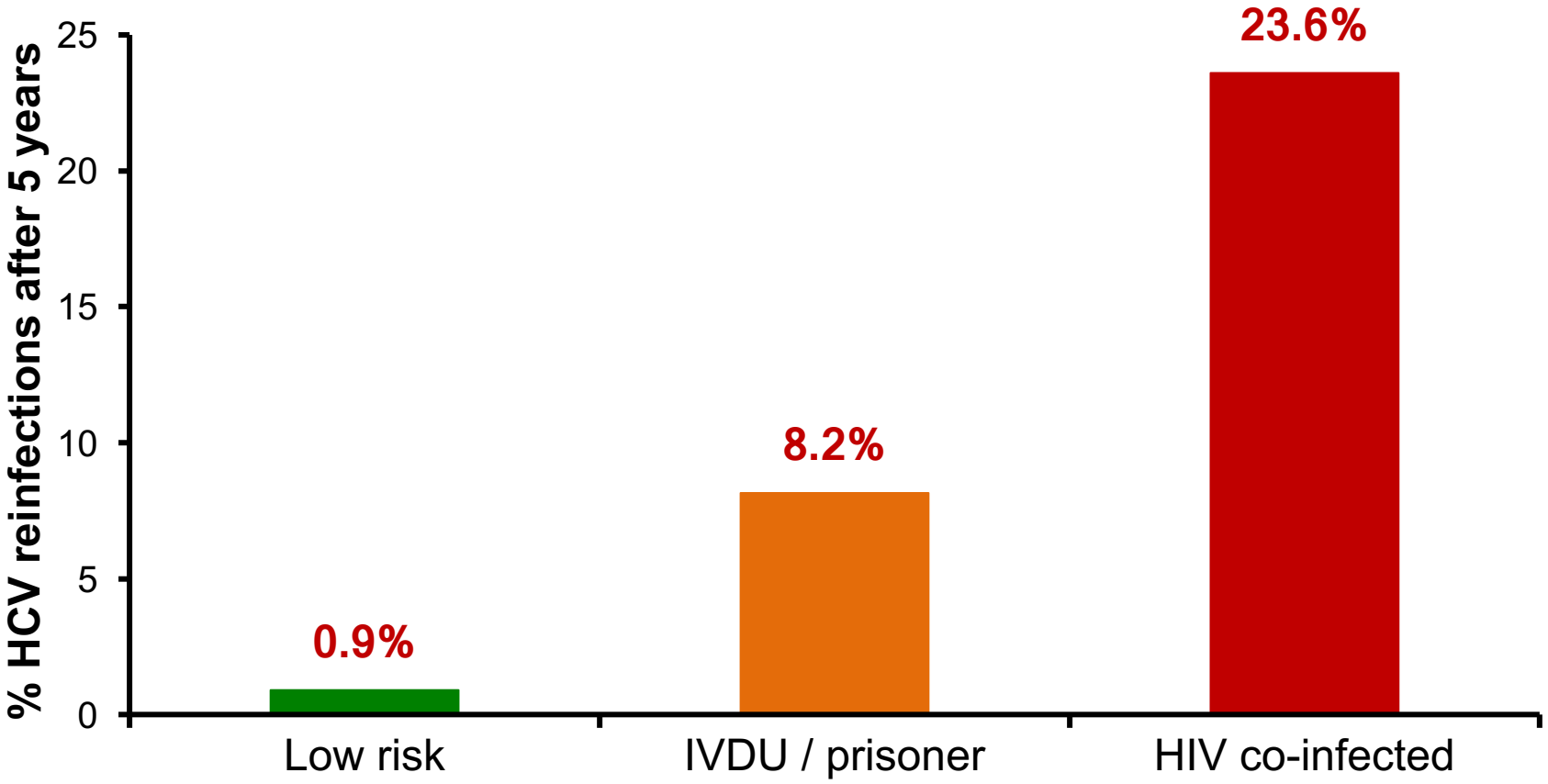


Five year risk of HCV re-infection post-SVR

Low-risk
24 studies
n=6,046
Avg. FU=4.1 years

IVDU / prisoners
16 studies
n=1,203
Avg. FU=5.0 years

HIV co-infected
10 studies
n=1,106
Avg. FU=3.1 years



Limitations

1. People with versus without SVR may differ in baseline characteristics, which could also affect outcomes. This potential bias was investigated by comparing results from univariate and multivariate analyses.

2. In the analyses of all-cause mortality for the general mono-infected cohorts, there was heterogeneity between the studies. This needs to be further investigated.

3. Results are shown for SVR after pegylated-interferon based treatment. We do not have data on long-term outcomes for SVR after DAA based treatment.

4. The absolute reductions in risk differ between cohorts, and depend on baseline age, HCV disease severity and other prognostic factors.

5. These results are shown for 5-year follow up. Longer-term predictions would be beyond the mean follow up time for most of the cohort studies in this analysis.

Conclusions

This analysis includes data on survival from 34,563 patients, followed up after SVR for a mean of 5 years.

Achieving SVR after interferon-based treatment for Hepatitis C, versus no SVR, was associated with:

- 62-84% reductions in the risk of all-cause mortality
- 90% reduction in the risk of liver transplantation
- 68-79% reductions in the risk of HCC

However there was a significant risk of subsequent re-infection after SVR in some studies, which could reverse these benefits of treatment.

These analyses need to be repeated for studies of Direct Acting Antivirals