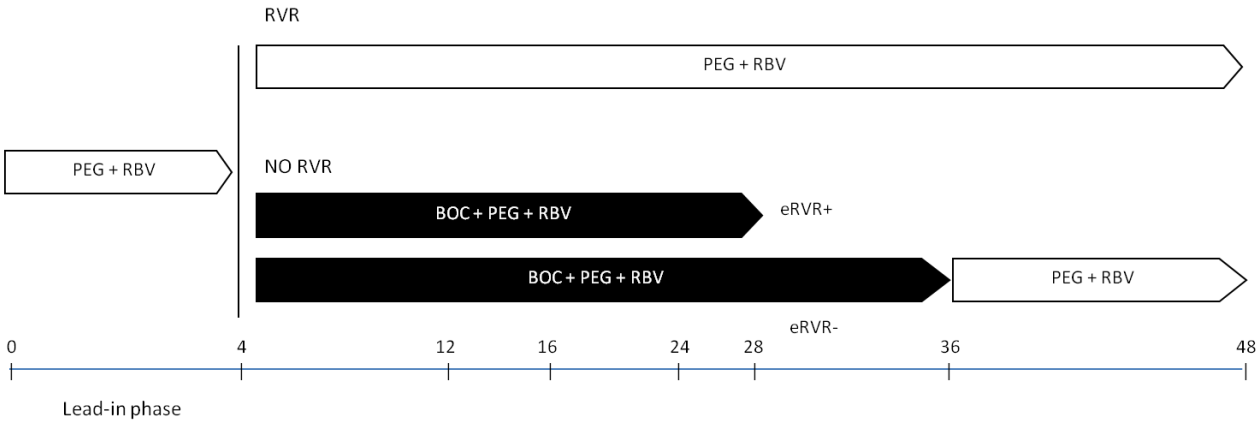
SUPPLEMENT 1

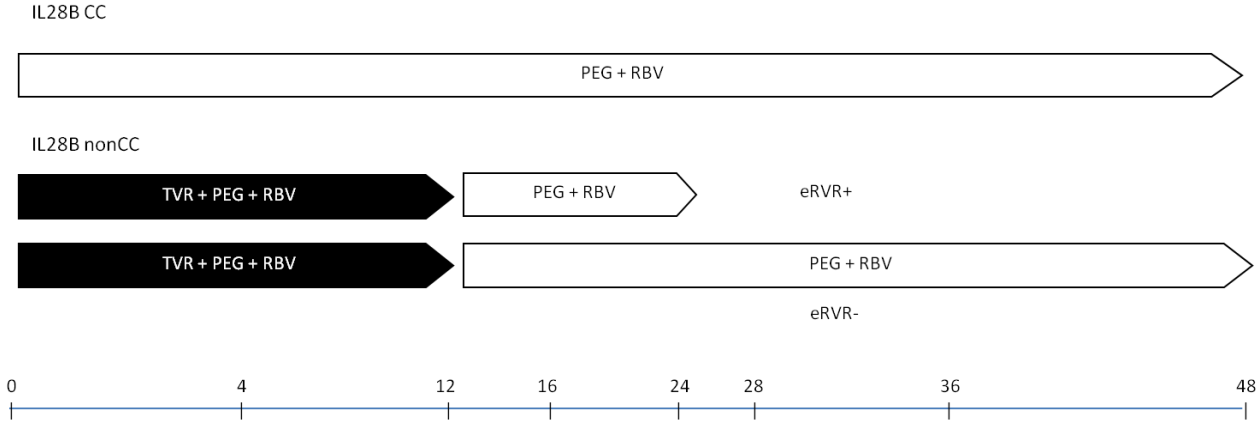
TREATMENT PROTOCOLS

BOC-RVR for G1 naïve CHC



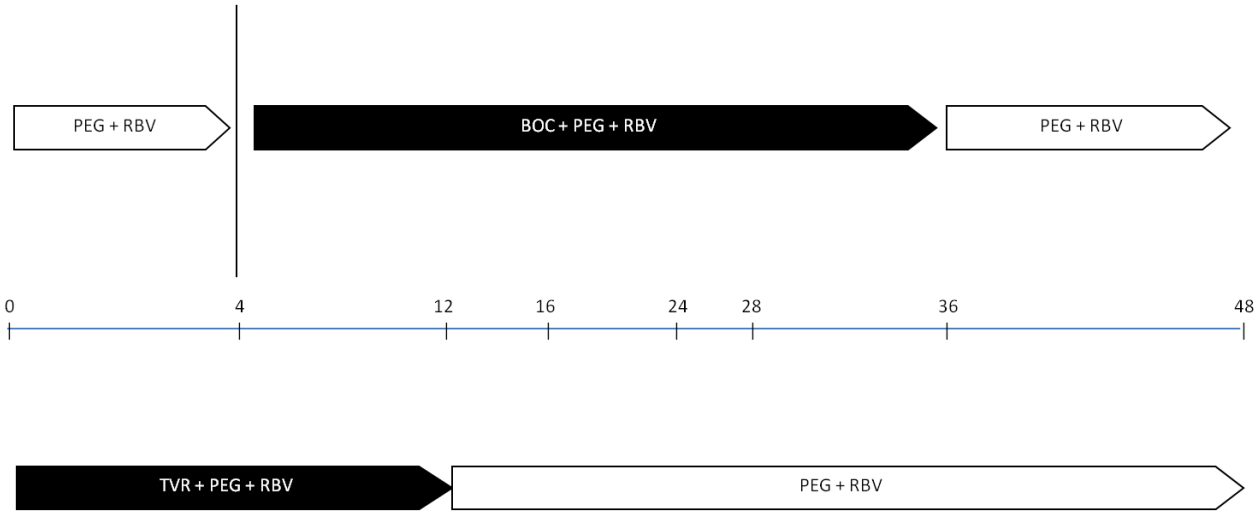
After a 4-weeks *lead-in* phase with peg-interferon plus ribavirin patients may achieve or not a RVR. The former continue on DT till 48th week while the latter are treated with a TT protocol whose length is determined by *on-therapy* response (eRVR, defined as HCV RNA not detectable at weeks 8-24). Patients who achieve a eRVR stop therapy at week 28. Patients who do not achieve eRVR continue TT till week 36 and then proceed with peg-interferon and RBV only till week 48. The subjects who achieve RVR but failed DT treatment, not achieving SVR, are re-treated with 32 weeks of TT plus 16 weeks of DT.

IL28B-guided TVR for G1 naïve CHC



IL-28B CC patients are directly assigned to DT. IL-28B nonCC patients are treated with a TT protocol where TVR is administered for the first 12 weeks in combination with peg-interferon and ribavirin. Patients who achieve eRVR (HCV RNA not detectable at weeks 4-12) continue DT till week 24, while patients with no eRVR continue DT till week 48. IL-28B CC patients, who do not achieve SVR after DT, are re-treated with 12 weeks of TT and 36 weeks of peg-interferon and ribavirin.

BOC and TVR treatment in F4 G1 CHC



Patients with cirrhosis are treated only with BOC- or TVR-based TT regardless of RVR or IL-28B status.

SUPPLEMENT 2

Transition probabilities from F4 to decompensated cirrhosis and from F4 to HCC were reassessed from a meta-analysis of Alazawi et al. [1]. This meta-analysis was aimed to establish the outcome of F4 HCV subjects by including thirteen cohorts, mainly prospective, conducted in Europe (n=8), USA (n=1) and Japan (n=4). In details, the aforementioned transition probabilities were computed by excluding from the meta-analysis non-European studies, i.e. the US one by Hu and Tong, and the four Japanese ones by Okanoue et al., Shiratori et al., Kobayashi et al and Toshikuni et al. Thus, the reassessed transition probability from F4 to decompensated cirrhosis was based on 6 European studies, leading to a total of 995 F4 HCV subjects of whom 359 developed a decompensation, with a transition probability of 0.04 (95% CI, 0.030-0.055). Similarly, the reassessed probability from F4 to HCC was based on 8 studies, leading to a total of 1,503 F4 HCV subjects of whom 321 developed HCC, with a transition probability of 0.03 (95% CI, 0.024-0.042).

The same algorithm was applied to derive the annual liver related mortality probability. Based on 7 European studies and on a total of 1,411 F4 HCV subjects, the reassessed annual liver related mortality probability of F4 HCV subjects was 0.03 (95% CI, 0.023-0.041).

Reference

1. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment Pharmacol Ther. 2010 Aug;32(3):344-55.

SUPPLEMENT 3

Effectiveness of treatment therapy by different fibrosis stage.

Treatment	Base case value (range)	Distribution	Reference
TVR IL-28B guided therapy			
F1, F2 and F3- Probability of eRVR	0.58 (0.53-0.64)	Beta	1
F1 and F2 - Probability of SVR with DT in IL-28 CC patients	0.72 (0.67-0.77)	Beta	2
F1 - Probability of SVR with TT	0.81 (0.74-0.88)	Beta	1
F1 and F2 - Probability of SVR with TT in retreated patients	0.73 (0.68-0.78)	Beta	3
F2 - Probability of SVR with TT	0.75 (0.67-0.82)	Beta	1
F3 - Probability of SVR with DT in IL-28 CC patients	0.41 (0.28-0.56)	Beta	2
F3 - Probability of SVR with TT	0.62 (0.47-0.75)	Beta	1
F3 - Probability of SVR with TT in retreated patients	0.57 (0.51-0.63)	Beta	3
F4 - Probability of SVR with TT	0.62 (0.38-0.82)	Beta	1
BOC RVR guided therapy			
F1, F2 and F3 - Probability of RVR	0.15 (0.14-0.16)	Beta	4
F1, F2 and F3 - Probability of eRVR	0.68 (0.61-0.74)	Beta	5
F1, F2 - Probability of SVR with DT in patients with RVR	0.86 (0.81-0.90)	Beta	6
F1 and F2 - Probability of SVR with TT in patient with no RVR	0.70 (0.64-0.75)	Beta	5
F1 and F2- Probability of SVR with TT in retreated patients	0.66 (0.57-0.64)	Beta	7
F3 - Probability of SVR with DT in patients with RVR	0.66 (0.60-0.86)	Beta	Assumption
F3 - Probability of SVR with TT in patient with no RVR	0.54 (0.45-0.64)	Beta	8
F3 - Probability of SVR with TT in retreated patients	0.44 (0.26-0.62)	Beta	7
F4 – Probability of SVR with TT	0.55 (0.44-0.66)	Beta	8
Reduction in SVR for F3 patients with RVR	0.229 (0-0.3)	Beta	Assumption

Reference

1. Jacobson IM, McHutchison JG, Dusheiko G, et al; ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416.
2. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010 Jul;139(1):120-9.e18.
3. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.
4. Romero-Gómez M, Planas R, Ampuero J, et al. Meta-analysis: pegylated interferon α-2a achieves higher early virological responses than α-2b in chronic hepatitis C. Aliment Pharmacol Ther. 2013 Jun;37(11):1065-73.
5. Poordad F, McCone J Jr, Bacon BR, et al; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206.
6. McHutchison JG, Lawitz EJ, Shiffman ML, et al; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.
7. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.
8. Vierling JM, Zeuzem S, Poordad F, et al. Safety and efficacy of Boceprevir/Peginterferon/Ribavirin (BOC/P/R) combination therapy for chronic HCV G1 patients with compensated cirrhosis: a meta-analysis of five phase 3 clinical trials. J Hepatol 2013; 58(S1): S567-S568.

SUPPLEMENT 4

Because different ribavirin and pegylated interferons are available in Italian market, an average unit cost has been estimated for these two classes of drugs and applied in the model. (AIFA - http://www.agenziafarmaco.gov.it/) Further, the dose of interferon and ribavirin are based on the patient' body weight and the association with TVR or BOC:

- the pegylated interferon a2b was administrated at a dose of 1.5 mcg per kilogram of body weight, while the interferon a2a was administrated at a dose of 180 gr per week.
- the ribavirin was administrated at a dose of 1000 mg per day in patients < 75 kg and 1200 mg in subjects ≥ 75 kg when associated to TVR; while at a dose of 800 mg per day in patients <65 kg, 1000 mg between 65 and 85 kg, 1200 mg between 86 and 105 kg and 1400 mg > 105 kg when associated to BOC.

To estimate the treatment cost, the different doses were applied in the model using the body weight distributions of our cohort (Table 4A). Because we assumed the same probability of using pegylate interferon a2a and a2b, an average cost of the two interferon treatments was applied to estimate to overall cost of the TVR and BOC protocol. The weekly treatment costs are showed in Table 4B.

Table 4A. VBMH naïve CHC G1 patients body weight distributions.

Body weight distribution	**Value**	**Source**
Percentage of patients with a BD < 75Kg	0.63	9
Percentage of patients with a BD < 65 Kg	0.36	9
Percentage of patients with a BD ≥ 65 and < 85 Kg	0.50	9
Percentage of patients with a BD ≥ 86 and < 105 Kg	0.14	9
Percentage of patients with a BD ≥ 105 Kg	0	9

Table 4B. Weekly treatment cost estimated using the body weight distributions of our cohort.

Treatment	**Weekly cost (€)**
Peginterferon alfa2a/b	€ 256.7
Ribavirin	€ 161.5
Boceprevir	€ 782.70
Telaprevir	€ 2083.25

SUPPLEMENT 5

Model validation

Our model presented several key differences from prior cost-effectiveness analyses. In particular, we characterized the cohort by 5 stages of METAVIR fibrosis with recognition that the prevalence of these stages and the mean ages associated with each of them may modify the overall survival of the cohort. Therefore, to validate the model we used a cohort of only F4 patients similar to that reported by Cucchetti et al. [1] In our model, the 1 and 5 year survival rates of patients with CC were 95.7% and 67.2%, respectively, while the 10 years life-expectancy was 6.5 years. These results are in agreement with the results from the model by Cucchetti et al. and the literature [1,2,3].

References

1. Cucchetti A, Trevisani F, Cescon M, et al. Cost-effectiveness of semi-annual surveillance for hepatocellular carcinoma in cirrhotic patients of the Italian Liver Cancer population. J Hepatol. 2012 May;56(5):1089-96.
2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–231.
3. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127:S35–S50.

SUPPLEMENT 6

Treatment protocols overall SVR % are reported in Table 6A, stratified by fibrosis stages. The results include the SVR get with the first treatment and the retreatment in the IL-28 CC and RVR patients that did not get SVR with DT.

Table 6A. Treatment protocols overall SVR %

Telaprevir IL-28B guided triple therapy	**SVR %**
F1	84.8%
F2	80.8%
F3	66.1%
F4	62.0%
Boceprevir RVR guided triple therapy	
F1	73.7%
F2	73.7%
F3	67.7%
F4	55.0%

SUPPLEMENT 7

The influence of parameters uncertainty on ICER as €/QALY and €/LYG are showed in the tornado diagrams reported below (Figure 7A-7H). Ten parameters that more influenced the ICER in the two protocol treatment are reported. The horizontal axis represents the ICER as €/QALY in the Figure 7A, 7B, 7E and 7F, and as €/LYG in the Figure 7C, 7D, 7G and 7H. The width of the bars illustrates the range ICER compared with F3-F4 patients' selection strategy. Upper and lower limits of values evaluated in sensitivity analysis are reported in Table 1 and 2 of the manuscript. The bars are ordered from the greatest width at the top to the least width at the bottom. The vertical dashed line represents the base case.

Figure 7A. Tornado diagram TVR IL-28B guide triple therapy: F1-F4 vs F3-F4.

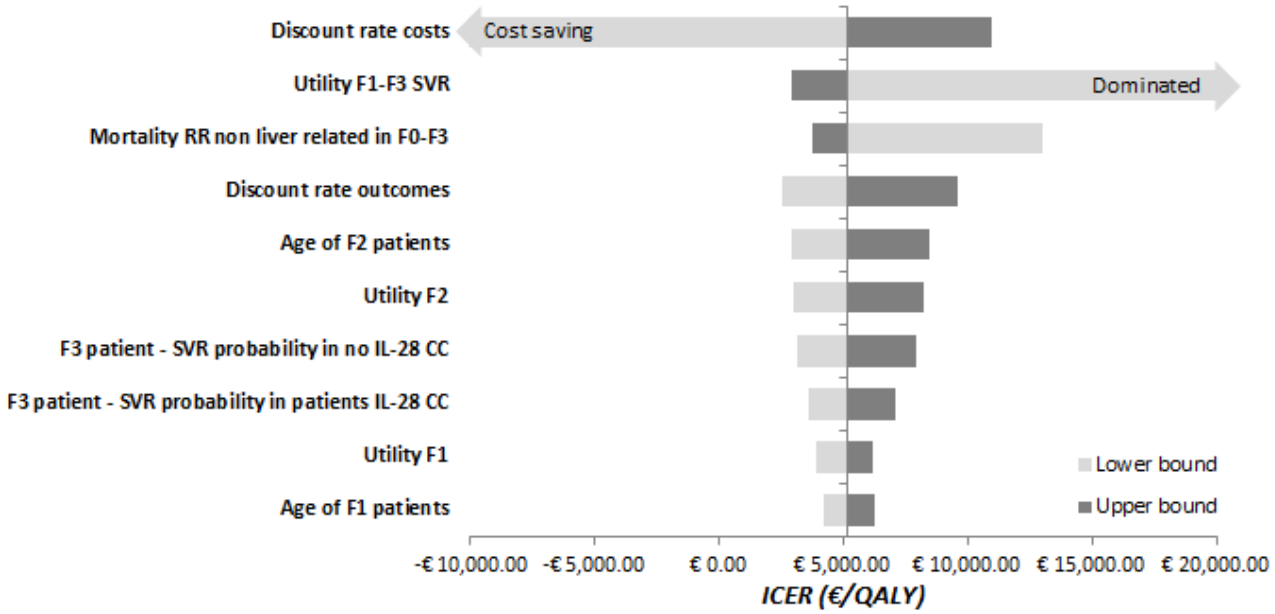


Figure 7B. Tornado diagram TVR IL-28B guide triple therapy: F2-F4 vs F3-F4.

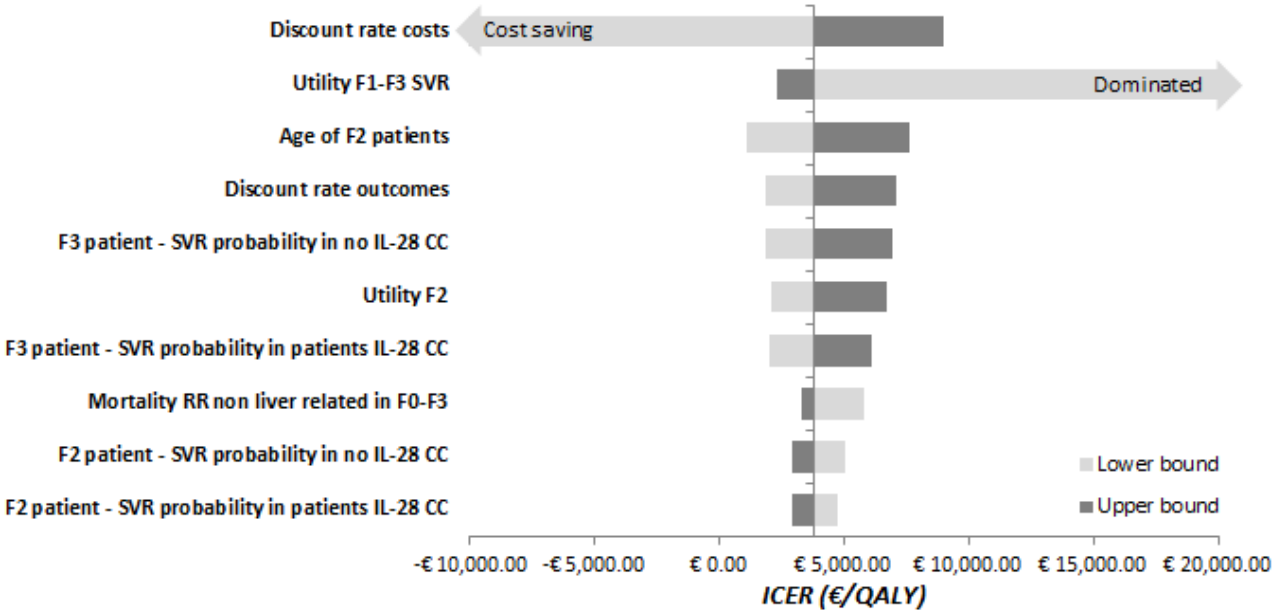


Figure 7C. Tornado diagram TVR IL-28B guide triple therapy: F1-F4 vs F3-F4.

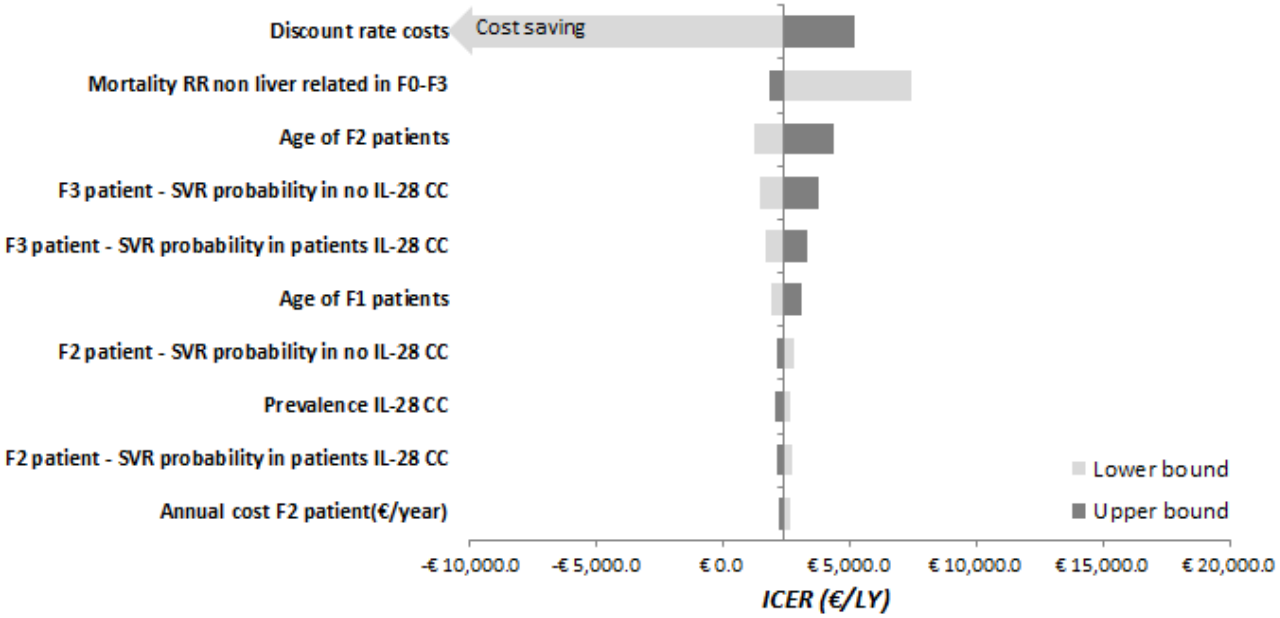


Figure 7D. Tornado diagram TVR IL-28B guide triple therapy: F2-F4 vs F3-F4.

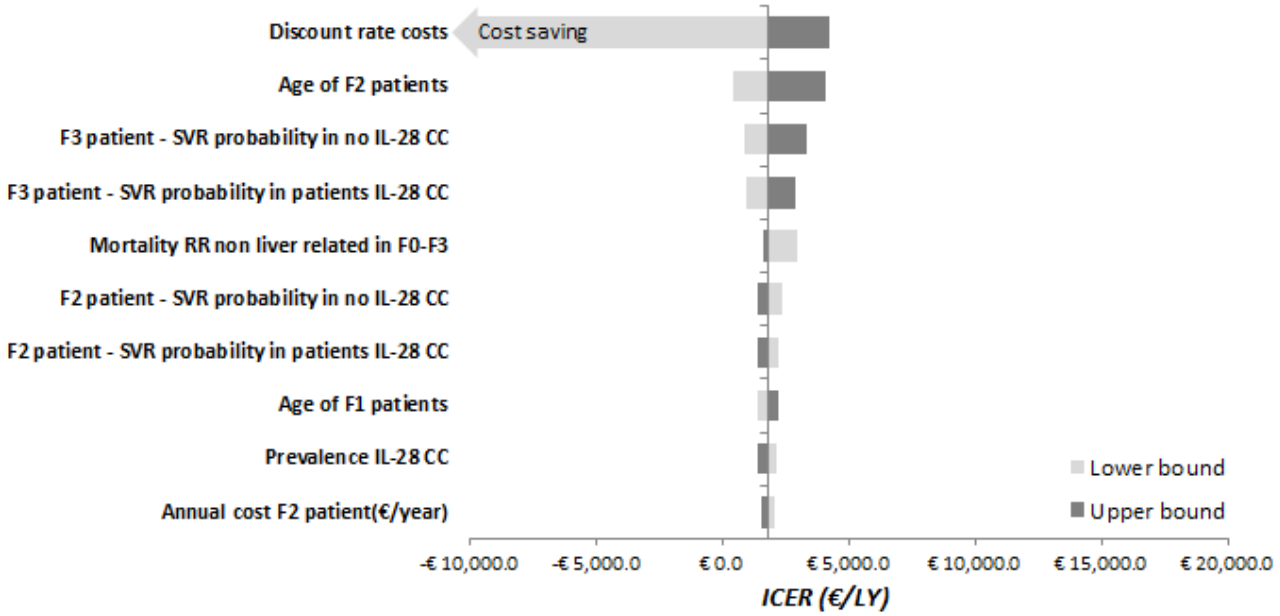


Figure 7E. Tornado diagram BOC RVR guide triple therapy: F1-F4 vs F3-F4.

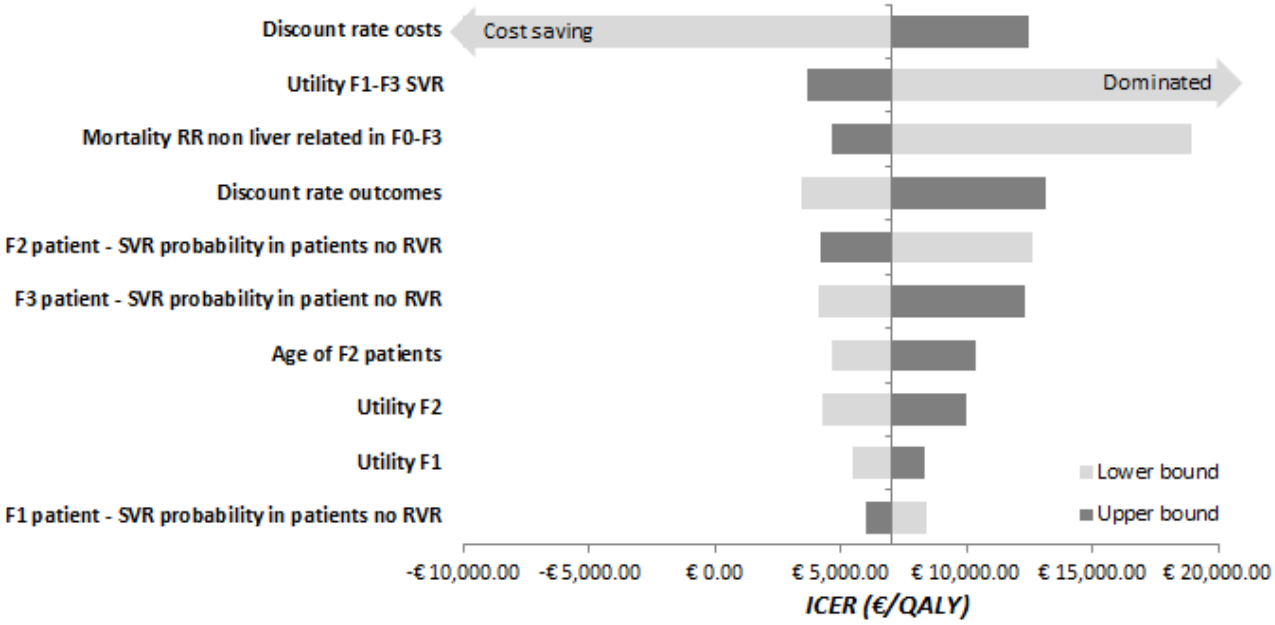


Figure 7F. Tornado diagram BOC RVR guide triple therapy: F2-F4 vs F3-F4.

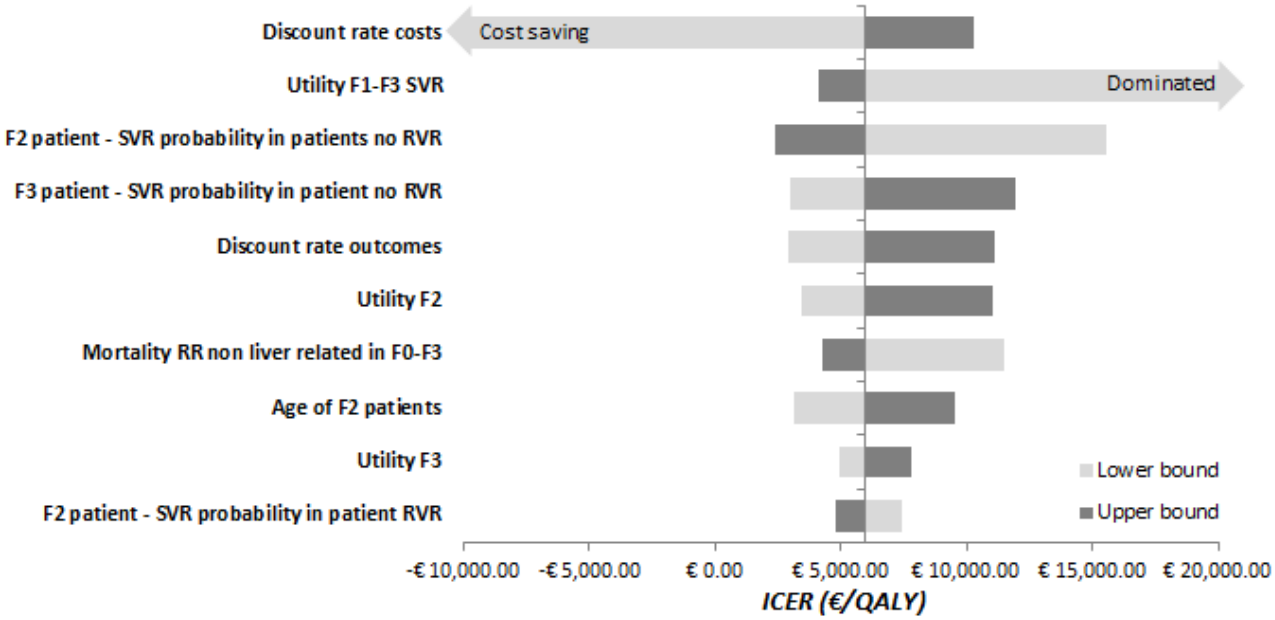


Figure 7G. Tornado diagram BOC RVR guide triple therapy: F1-F4 vs F3-F4.

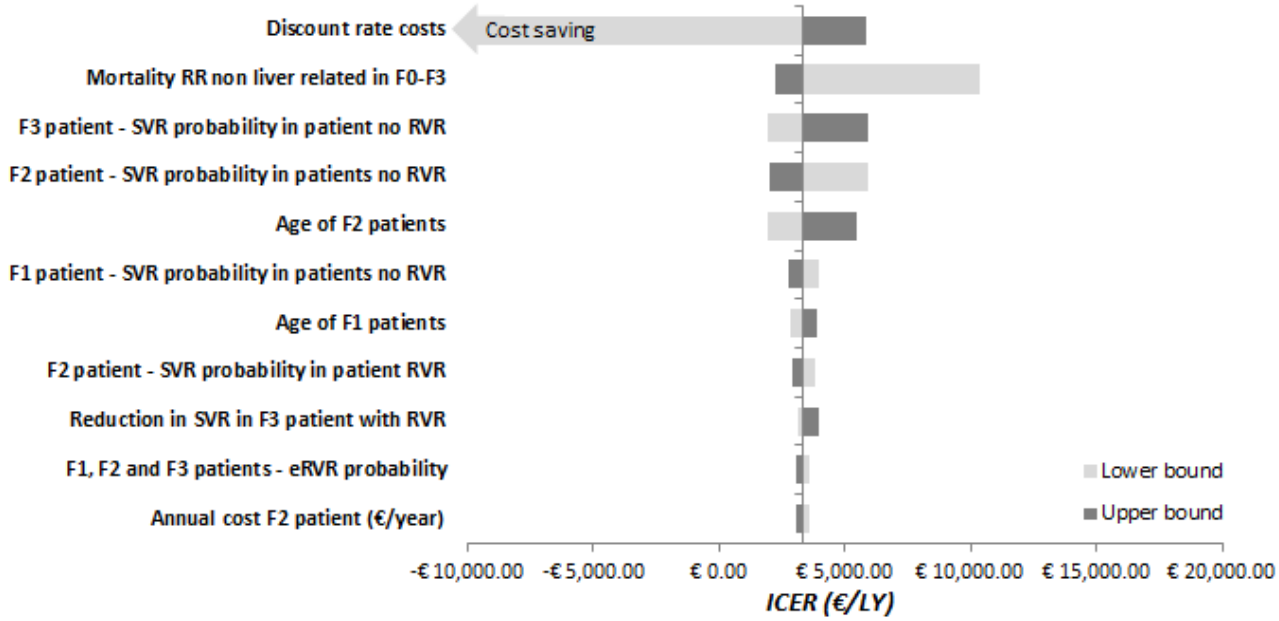
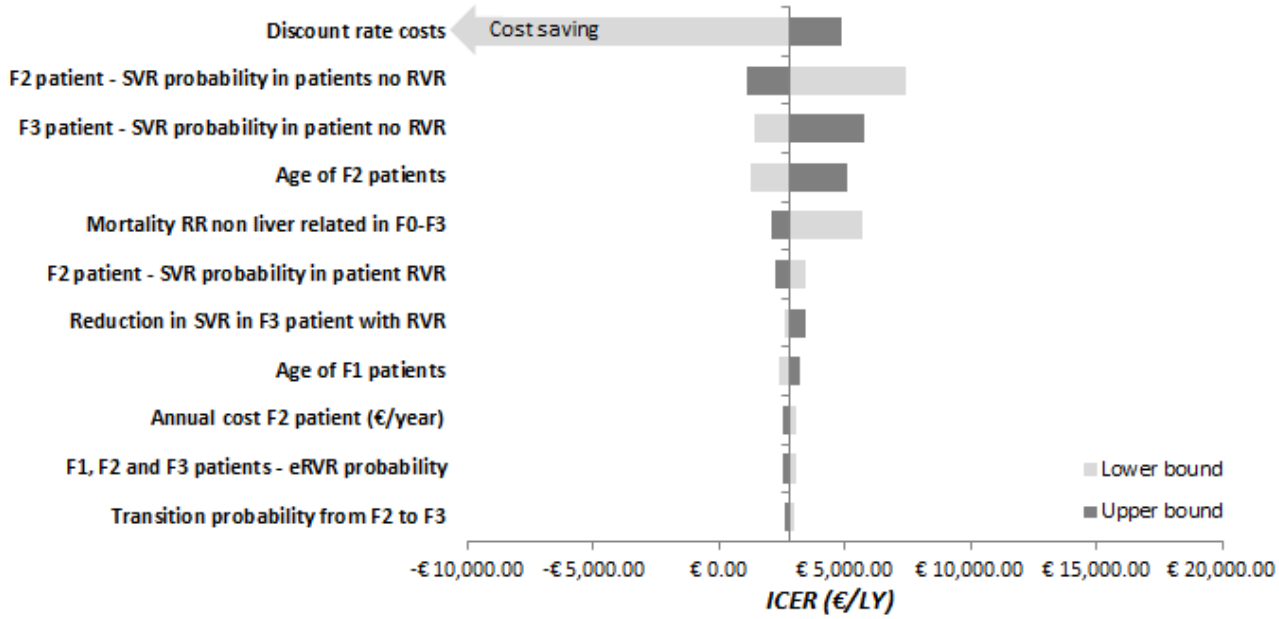


Figure 7H. Tornado diagram BOC RVR guide triple therapy: F2-F4 vs F3-F4.



Using the fibrosis stages reported by Poynard et al. (F0=15.6%, F1=38.8%, F2=19.0%, F3=14.1%, F4=12.5%), [1] we assessed the influence of different fibrosis stage distribution on the model results. The results reported below show a small impact of the fibrosis stages distributions on the results.

TVR IL-28B guided therapy

F1-F4 strategy vs F3-F4 strategy

Poynard distribution: ICER = € 7,824.23 per QALY and € 3,513.54 per LYG

Base case distribution: ICER = € 5,132.13 per QALY and € 2,426.62 per LYG

F2-F4 strategy vs F3-F4 strategy

Poynard distribution: ICER = € 4,475.48 per QALY and € 1,966.67 per LYG

Base case distribution: ICER = € 3,798.43 per QALY and € 1,800.11 per LYG

BOC IL-28B guided therapy

F1-F4 strategy vs F3-F4 strategy

Poynard distribution: ICER = € 9,904.54 per QALY and € 4,451.25 per LYG

Base case distribution: ICER = € 7,042.49 per QALY and € 3,326.88 per LYG

F2-F4 strategy vs F3-F4 strategy

Poynard distribution: ICER = € 6,484.67 per QALY and € 2,837.40 per LYG

Base case distribution: ICER = € 5,944.90 per QALY and € € 2,798.91 per LYG

Reference

1. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-832.