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Value and innovation of direct-acting antivirals: long-term health outcomes of the strategic plan for the management of hepatitis C in Spain

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ABSTRACT

Objective: To assess the long-term healthcare costs and health outcome in association with the access to new direct-acting antivirals (DAAs), during the first year of the National Strategic Plan for Chronic Hepatitis C (SPCHC) in patients with chronic hepatitis C (CHC) in Spain.

Methods: A decision tree and a lifetime Markov model were developed to simulate the natural history, morbidity, and mortality of a cohort of 51,900 patients with CHC before (pre-DAA strategy) and after (post-DAA strategy) access to DAA, following SPCHC approval. The percentage of patients treated, transition probabilities, disease management costs, health state utility values, sustained virologic response rates and treatment costs were obtained from the literature and published data from Spain. The results were expressed in terms of costs (€, 2016), quality-adjusted life years (QALYs) and prevention of clinical events, with an annual discount rate of 3%.

Results: The post-DAA strategy would prevent 8,667 cases of decompensated cirrhosis, 5,471 cases of hepatocellular carcinoma, 1,137 liver transplants and 9,608 liver-related deaths. The cohort of 51,900 patients would require investments of 1,606 and 1,230 million euros with the post-DAA and pre-DAA strategies, respectively. This would produce 819,674 and 665,703 QALYs.

Conclusions: The use of new DAA-based treatments in CHC patients during the first year after the implementation of the SPCHC significantly reduced long-term morbidity and mortality and increased quality of life; demonstrating that this plan is an efficient use of public health resources.

Key words: Direct action antiviral agents. Chronic hepatitis C. Strategic plan for hepatitis C management. Social value. Innovation. Efficacy.

INTRODUCTION

Studies performed before the implementation of the National Strategic Plan for Chronic Hepatitis C (SPCHC) estimated that the prevalence of hepatitis C virus (HCV) infection in Spain was 1.6%. This corresponds to approximately 475,000 people, of whom only 40% were diagnosed (1). Chronic hepatitis C (CHC) is characterized by the development of liver fibrosis, which leads to liver cirrhosis in up to 25% of patients (2). In most cases, this progression is slow and completely asymptomatic. However, once liver cirrhosis develops, the annual probability of developing clinically decompensated cirrhosis (DC) is 4% and the probability of developing hepatocellular carcinoma (HCC) is 1.5% (3). These conditions could eventually require liver transplantation (LT) or result

in death. Additionally, the delayed diagnosis and treatment of CHC facilitates viral transmission among the population.

From 1990 to 2013, the worldwide mortality rates related to cirrhosis and HCC caused by hepatitis C increased by 67% and 291%, respectively (4). Therefore, HCC resulting from CHC represents a major health burden (5) and is now among one of the eight pathologies that cause over 100,000 annual deaths worldwide. In Spain, the estimated number of total deaths attributable to HCV infection was 4,342 in 2000 from a total of 360,391 deaths (6), accounting for 1.5% of the deaths in that year. A premature death represents a quantifiable loss of life years. In 2006, the burden of CHC in Spain in terms of years of life lost ranged from 63,753 to 73,790 years (7). Therefore, CHC was the seventh leading cause of years of life lost. Moreover, when life years with disability are added to years of life lost, the resulting disability-adjusted life years (DALYs) loss ranges from 71,122 to 81,336 (7).

The efficacy of oral antiviral therapies based on pegylated IFNα (peg-IFN) that have been developed during the last decade has had a relatively low impact on the burden of HCV infection (8). Modeling studies conducted using data from a Spanish population evaluated outcome following the use of peg-IFN and ribavirin (peg-IFN/RBV) or triple therapy with an HCV protease inhibitor (boceprevir or telaprevir) and peg-IFN/RBV. This study showed that there were reductions in mortality (ranging from 8.1% to 10.3%) and cirrhosis incidence (ranging from 13.8% to 18.4%) only in patients infected with genotype 1 HCV (9).

The burden of CHC in Spain requires the use of innovative health interventions with improved efficacy and safety, such as new direct-acting antiviral agents (DAAs) in peg-IFN free regimens. These therapeutics have achieved > 95% infection cure rates (10-12) and have the potential to rapidly reduce the burden of the disease.

In Spain, the institutional response to the introduction of new DAAs regimens aimed to ensure access to treatment in a way that remains sustainable for the health system. These goals were pursued via the development and rapid implementation of the SPCHC in 2015 (13). The SPCHC states that all patients are eligible for high-effective DAA therapy. However, due to the extent of the disease in Spain, it was decided that patients with advanced liver fibrosis (including stages F2-F4), patients on transplant

waiting lists and those with recurrent HCV infection should be prioritized for these treatments. Other European countries have implemented similar measures to strategically prioritize patients for DAAs treatment by categorizing them into subgroups (14).

Given that economic resources are limited and that the sustainability of public health systems must be ensured in decision-making, it is necessary to evaluate the clinical evidence and cost-effectiveness of innovative therapeutics. When assessing treatment priorities, the principal question that must be addressed in an economic evaluation is whether the overall costs of an intervention are sufficiently counterbalanced by the health outcomes achieved. These factors should always be compared with the standard alternatives that are available at the time of decision-making. In addition, patient clinical characteristics (15,16) must be considered as well as the economic and National Healthcare System of each country (17). To address these issues, we first assessed the extent to which new DAAs prevent the hepatic complications of disease progression (e.g., DC, HCC, LT, and liver disease-related mortality). It is also important to evaluate the corresponding direct and indirect costs and the healthcare and non-healthcare resources used by patients with and without a sustained virologic response (SVR) to HCV therapy; such as patients without access to treatment or for whom treatment was not effective (18).

The aim of this study was to evaluate long-term health costs and outcomes during the first year (2015) after application of the SPCHC using new DAAs (post-DAA) in patients infected with CHC (≥ F2) from the perspective of the National Health System in Spain. These data were compared to those obtained when using previously available regimens (pre-DDA).

METHODS

The incremental long-term health outcomes and costs generated in CHC patients using new DAAs during the first year (2015) after implementation of SPCHC (post-DAA strategy) were compared to those using previously available regimens based on peg-interferon plus ribavirin and telaprevir or boceprevir prior to the SPCHC (pre-DAA strategy).

The analysis included 51,900 CHC patients with significant or advanced fibrosis (≥ stage F2) (13) with an average age of 52 (19). All patients were treated according to the European Medicines Agency (EMA) approved combinations of DAAs IFN free regimens (13). A decision tree was designed and patients were separated based on whether they were treated or untreated and were proportionally distributed according to their clinical characteristics (genotype, degree of fibrosis, treatment-naïve or previously treated status) (Table 1). The tree was used to calculate the global SVR rates for each fibrosis stage, regardless of genotype. In total, 73% of the patients were treated using the post-DAA strategy and 19% were treated with the pre-DAA strategy (20). SVR rates according to clinical characteristics were obtained from clinical trials or the most relevant studies of each treatment included in the analysis (21). The remaining patient clinical characteristics included in the decision tree were obtained from the literature and published Spanish data and are shown in table 1.

A lifetime Markov model was developed based on previously validated models (19,21) in order to project and analyze disease progression; during which patients could have transitioned annually from one stage to another depending on the probabilities of developing DC or HCC, undergoing LT or moving to post-LT status. Disease progression was monitored until death. Annual probabilities were obtained from the literature (22,24,29) (Table 1). SVR patients with stage F2 fibrosis were considered as no longer at risk of disease progression, whereas those with stage F3 or F4 fibrosis remained at risk of developing DC or HCC. In addition, according to the published data, the achievement of an SVR following treatment in cirrhotic patients could lead to the fibrosis regression (23). Therefore, this transition was considered in the simulation of disease for patients in the SVR F4 state. The patient quality of life for each health state is represented by utility measures obtained from the literature (24). Disutility was also considered during treatment administration (30) (Table 1).

With regard to the pharmacological cost of the pre-DAA strategy, an average cost of €15,003 per patient was calculated (31) within the Spanish health system, including the application of corresponding deductions. For the post-DAA strategy, the overall pharmacological cost of treating all patients with CHC in 2015 with the new DAA strategies was €1,094 million (32). For both strategies, the average cost of treatment

monitoring was €1,257 for the post-DAA strategy and €2,371 for the pre-DAA strategy. These costs included different treatment durations (8, 12, 24, or 48 weeks) and were calculated from published data (33). The annual health costs associated with each health state were obtained from published data (30,33). All costs are expressed in Euros and were updated in 2016.

Analysis of health costs and outcomes

Health outcomes were measured in terms of quality-adjusted life years (QALYs), which were calculated by multiplying the years of life gained with each strategy by the utility value. This measure reflects a patients´ preference for each health state (34). The incremental cost was calculated as the difference in total cost (drug, monitoring, and management of complications) between one strategy and another.

In order to calculate the present value of future costs and health outcomes and compare them in terms of a net present value, a discount rate of 3% was applied (35). However, there is a lot of debate regarding whether health outcomes and cost should be discounted, the rate and time point. Cost data and health outcomes without the discounted rate (0%) applied have also been included in some cases (36).

In order to provide a monetary estimate of the societal value of quality of life adjusted survival gain, the number of incremental QALYs obtained with the post-DAA strategy versus the pre-DAA strategy was multiplied by different values of cost per QALY or willingness to pay (37), such as 20,000, 25,000 and 30,000 euros per QALY (37,38).

Sensitivity analysis

Different one-way sensitivity analyses (OWSA) were performed for each minimum and maximum value for the parameters that generated a greater uncertainty of the analyzed results. These parameters included the SVR rates for each fibrosis stage when the values obtained in the decision tree were considered (87.4-93.2% for post-DAA and 55.0-75.2% for pre-DAA) and also the ranges of values of the percentage of patients treated (66-100% for post-DAA and 17-21% for pre-DAA), drug costs (± 20%) and LT costs (± 20%).

RESULTS

Figure 1 shows the overall cost and health outcome expressed as QALYs for the 51,900 patients evaluated. The incremental cost of the post-DAA strategy compared with the pre-DAA strategy is €375 million. For the period in which access to new DAAs was considered (i.e. during the first year of SPCHC implementation), 153,970 additional QALYs were obtained with the post-DAA strategy compared to the pre-DAA strategy.

After disease modelling of the cohort, the post-DAA strategy would avoid 8,667 (63%) cases of DC, 5,471 (53%) cases of HCC, 1,137 (59%) LTs and 9,607 (58%) liver disease-related deaths compared to the pre-DAA strategy. This would save approximately €468 million, 84% of these savings would result from the reduced number of LTs and cases of HCC following the post-DAA strategy (Table 2). The number of avoided events and their associated costs without a discount rate applied are shown in table 2 and figures 2 A-D.

After running the model for 10 years without applying a discount rate and using the post-DAA strategy, 64% of the total cohort (51,900) had achieved a SVR, 2.2% had DC, 1.1% had HCC and 5.3% had died from liver-related causes. Significantly fewer patients from the total cohort achieved a SVR at 10 years (10.5%) with the pre-DAA strategy. The proportion of patients with DC or HCC increased to 6.0% and 2.5%, respectively and the mortality rate associated with liver disease was 11.6% (Figures 3 A and B).

Estimation of the monetary value of a QALY (cost per QALY: 20,000, 25,000 and 30,000 euros)

The monetary value of the incremental QALYs achieved with the post-DAA strategy *versus* the pre-DAA strategy within the cohort using the number of incremental QALYs of the baseline case (Fig. 1) ranged from 3,079 to 4,619 million euros. The value per QALY was between 20,000 and 30,000 euros (Fig. 4).

Sensitivity analysis results

The QALY values ranged between 135,607 and 220,701 additional QALYs when the OWSA was used to compare the post-DAA and pre-DAA strategies. The incremental cost ranged between 156 and 594 million Euros. Drug costs had the greatest influence

on the results in the post-DAA strategy, which amounted to €218 million. In contrast, drug cost had a lower impact in the pre-DAA strategy (€29 million). As all patients in the post-DAA strategy group were treated, the increment QALY gain was 220,701 which was associated with an incremental cost of €531 million. Modification of the percentage of patients treated in the pre-DAA strategy did not significantly alter the results of the analysis. When minimum values of SVR rates were considered, 141,381 and 160,285 QALYs were obtained for the post-DAA and pre-DAA strategies, respectively. Variations in the cost of transplantation were not associated with significant variations in incremental cost (€27 million).

DISCUSSION

The introduction of oral DAA regimens to treat CHC has changed the management of this disease (40). The high efficacy and safety of DAAs allow any HCV-infected patient to be treated and eventually cured (40). The present analysis evaluated long-term health outcomes and costs following the implementation of the SPCHC in 2015. The results demonstrate that the prevention of clinical events related to liver disease and the costs associated with their management and the increased quality-adjusted life years compensate for the financial investment in drug costs.

Health resources are limited and must be managed in a manner consistent with the needs of a population to ensure the sustainability of a health system. One way to manage these resources is using value-based health systems, which have a fundamental objective of achieving the best health outcome for patients at an acceptable and sustainable cost. For this to occur, measures must be adopted based on value and this value is defined from the result obtained per monetary unit invested. These measures include estimating disease cost, improving and innovating health technologies, ensuring patient access to innovative treatments with disruptive changes over health outcomes and improving the general health of the population.

It should be noted that the costs of CHC treatment only corresponded to the first year following the implementation of the SPCHC, as the objective of this analysis was to evaluate health outcomes in 2015. The analysis only took into account the investment

already made and not the cost of continuing the SPCHC. As more patients are treated, this cost will decrease for various reasons, including reductions in the number of patients eligible for treatment due to the decreased disease prevalence that results from the high treatment efficacy of new DAAs, as well as reductions in treatment costs. This phenomenon has already been reflected in the CHC drug expenditure corresponding to the second half of 2016, which was 63% lower than that in 2015 (41). To measure the impact of drug cost change on analysis results, an OWSA was performed in which drug costs were varied for each treatment strategy (pre-DAA and post-DAA). The results of the analysis showed an incremental cost of €218 million. Therefore, the predicted lower drug cost in the future would reduce the incremental cost and increase the efficiency of the continuation and/or extension of the treatment strategies presented in the SPCHC.

The effectiveness of new DAAs in treating CHC is evident and there is a strong level of evidence supporting their use in clinical practice. However, whether the budgetary impact derived from the use of DAAs translates into a worthwhile investment for health systems needs to be assessed. It is important to consider that patients with CHC who were treated with new DAAs achieved SVR rates of > 95% (10-12,18), indicating that most were cured and that investing in drugs to treat CHC might be worthwhile.

Another important factor associated with value systems is innovation. In this regard, the measurement and comparison of health outcomes with those obtained from previous strategies is essential (42,43). The new DAAs have contributed to an increase in treatment efficacy and effectiveness, a greater tolerability and adherence by patients, a shortening of treatment duration and a simpler dosage regimen, which is particularly innovative. However, evaluating the efficiency of innovation requires the estimation and association of the cost of innovation, which is the relationship between the increased SVR rates produced by the new DAAs and their cost in this case (44). This relationship must be established and compared to drugs previously used as standard therapies. In our analysis, the post-DAA strategy implemented in the SPCHC was more cost-effective than the pre-DAA strategy from a clinical standpoint.

The reduced number of LTs for the patients who were cured in 2015 represents a savings of €509 million, which corresponds to an overall saving of 65% of CHC follow-

up and complication treatment costs. However, these results may underestimate the actual effect, as new evidence suggests that eliminating HCV in patients already on LT waiting lists might lead to significant improvements in liver function, ultimately resulting in patients being withdrawn from the waiting list (45). A collateral benefit of the reduction in LTs for patients with CHC is the increase in availability of livers for organ donation for other indications (46). In Spain, 36.4% of all LTs in 2015 were performed in cirrhosis patients due to HCV and HCC (47). As the new DAAs prevent CHC from progressing to more advanced stages, according to our analysis, the number of transplants would be expected to be reduced by 46.2% over the next 10 years.

Our analysis also focused on the monetary value of the post-DAA strategy by extrapolating the QALYs achieved by the post-DAA strategy compared to the pre-DAA strategy (48). This approach has been used in other health evaluations such as the study by Van Nuys et al., which evaluated the social benefit in monetary terms from the QALYs obtained with new DAAs and from different values assigned to the efficiency threshold in the treatment of HCV-infected patients in the United States (37). In the present study, the monetary value associated with the increase in QALYs achieved with the post-DAA *versus* pre-DAA strategy (153,981 QALYs) across the patient cohort ranged from 3,069 to 4,604 million Euros. This far exceeds the cost increase of €375 million.

In the SPCHC, patients who should have preferential access to the new DAAs are defined as those with significant fibrosis (≥ F2) and those whose treatment cannot be deferred. The total number of patients estimated to receive treatment was 51,900, and approximately 73% of these patients were treated in 2015 and the remainder was treated at the beginning of 2016. A more accurate assessment would require real observed data of SVR rates obtained from the SPCHC and the evaluation of access for all infected patients, including those in the initial stages of fibrosis. This study did not include patients in stage F0 or F1 as this was not the objective of the study. Future pharmacoeconomic studies must include all infected patients in Spain in order to evaluate the overall clinical and economic impact of the new policies. Furthermore, as our analysis focused on the current population of patients who had already received treatment, the development and implementation of screening programs for the

detection of HCV in high-risk groups in order to enable their access to curative treatment should be examined in future revisions of the SPCHC. On the other hand, the model used in this this study focused only on the first year following the implementation of the SPCHC and the extra-hepatic manifestations associated with CH. These occur irrespective of the stage of liver disease (49) and could increase the total disease burden, which has not been taken into account (50). Had these situations been considered, the difference in efficacy and safety between previous and new antivirals would probably have shown a greater clinical benefit by preventing a greater number of liver complications and also extra-hepatic complications within the CHC population.

Another factor that should be considered is the fact that this analysis was conducted from the perspective of the National Health System and not from a societal perspective. Thus, the productivity loss of CHC patients was not considered. This is relevant as the CHC population is mostly a working age population (50). Prior studies on work productivity associated with HCV infection have confirmed that CHC patients show high rates of absenteeism and that their work productivity significantly deteriorates (50). This deterioration does not affect treated and untreated patients equally as different treatments impact to a greater or lesser extent on productivity due to the variability in adverse events. In economic terms, this translates into increased indirect costs resulting from lost working hours as well as increased direct costs due to factors such as increased consumption of health resources (50). These costs may be added to the cost of premature deaths due to CHC, which has been estimated at €1,054 million over a period of three years (51). Only direct costs were incorporated in our analysis and any costs associated with the loss of productivity were excluded. Had these latter costs been included, it would have significantly increased the total cost of the pre-DAA strategy due to the low percentage of patients treated and their poorer health status compared with those treated with the post-DAA strategy.

CONCLUSION

To ensure the sustainability of the healthcare system, prioritizing care for patients in more advanced stages of disease is crucial and the subsequent establishment of a

treatment strategy for all patients, regardless of their fibrosis stage. The present economic evaluation demonstrates that the use of DAA-based treatments for CHC patients in Spain would significantly reduce the morbidity and mortality associated with the disease and thus represents an efficient use of public resources. Despite the initial disbursement allocated to the acquisition of new treatments, the current treatment strategy for the population classified as a priority in the SPCHC (post-DAA) increases long-term societal value and guarantees sustainability of the National Health System.

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Table 1. Parameters used in the modelling of chronic hepatitis C

Parameter		Value	Reference
Distribution of patients according to their characteristics			
Genotype			
GT 1, %		69.32	(13)
GT 2, %		2.27	(13)
GT 3, %		15.91	(13)
GT 4, %		12.50	(13)
Fibrosis stages			(13)
F2, %		31.48	(13)
F3, %		27.78	(13)
F4, %		40.74	(13)
Treatment status			
Naïve, %		41.42	(19)
Pretreated patients, %		58.58	(19)
Estimated SVR rates			
Fibrosis stages	Pre-DAA (ranges)	Post-DAA (ranges)	
F2, %	55.0 – 75.2	93.9 – 97.1	Calculated from register studies or trials
F3, %	55.0 – 75.2	93.2 – 96.9	
F4, %	55.0 – 75.2	87.4 – 96.3	

Annual transition probabilities	Value	Reference
F2 - F3	0.12	(23)
F3 - F4	0.116	(23)
F3 - HCC	0.011	(28)
SVR F3 - HCC	0.00264	(28)
F4 – DC	0.04	(27)
F4 - HCC	0.015	(22)
SVR F4 - DC	0.003	(28)
SVR F4 - HCC	0.005	(28)
SVR F4 - Regr. HC	0.055	(25)
DC - HCC	0.068	(26)
DC - LT	0.023	(24)
DC - Liver-related death	0.138	(26)
CHC - LT	0.04	(24)
CHC - Liver-related death	0.43	(22)
LT - Post-LT	1.00	Assumption
LT - Liver-related death	0.21	(22)
Post-LT - Liver-related death	0.057	(22)

	Annual health state utility values		Cost of the health states	
Health states	Utility values	Reference	Costs	Reference
F2	0.92	(23)	€305	(32)
F3	0.79	(23)	€305	(32)
F4	0.76	(23)	€556	(32)
SVR F2 (1st year)*	0.93	(23)	€112	(27)
SVR F3 (1st year)*	0.86	(23)	€112	(27)
SVR F4 (1st year)*	0.83	(23)	€161	(27)
Regr. HC	0.86	(23)	€112	(27)
DC	0.69	(23)	€2,265	(32)

HCC	0.67	(23)	€8,629	(32)
LT	0.50	(23)	€121,707	(32)
Post-LT	0.77	(23)	€35,574	(32)

The cost of SVR states in subsequent years was €0.00 (SVR F2), €0.00 (SVR F3) and €161.70 (SVR F4). DAA: Direct-acting antiviral; DC: Decompensated cirrhosis; GT: Genotype; HCC: Hepatocellular carcinoma; LT: Liver transplant; Post-LT: Post-liver transplant; Regr. HC: Regression of hepatic cirrhosis; SVR: Sustained virologic response.

Table 2. Clinical events avoided and cost savings (€, 2016) as a consequence of avoiding events with the post-DAA versus pre-DAA, with (3%) and without (0%) the discount rate for costs and outcome

Clinical event	Events (post-DAA)*	Total cost of events (post-DAA)	Events (pre-DAA)[†]	Total costs of events (pre-DAA)
Discount rate results (3% for costs and outcomes)				
Decompensated Cirrhosis	5,112	€42,925,048	13,779	€118,877,981
Hepatocellular carcinoma	4,781	€82,200,386	10,252	€181,274,045
Liver transplantation[§]	793	€196,329,404	1,930	€489,452,403
Liver-related death	6,792	-----	16,400	-----
Total		€321,454,838		€789,604,429
Results without discount rate (0% for costs and outcomes)				
Decompensated cirrhosis	7,872	€70,021,521	21,465	€190,254,533
Hepatocellular carcinoma	7,403	€129,445,520	16,136	€281,720,163
Liver transplantation[§]	1,311	€351,493,029	3,237	€861,443,958
Liver-related death	11,272	-----	27,659	-----
Total		€550,960,070		€1,333,418,654

*In the post-DAA strategy, 73.4% of the patients were treated and 26.6% of the patients did not receive treatment. [†]In the pre-DAA strategy, 18.9% of the patients were treated and 81.1% of the patients did not receive treatment. [‡]Cost savings as a consequence of avoiding events with the post-DAA strategy versus the pre-DAA strategy during the 50 year modelling in a cohort of 51,900 patients with HCC. [§] Transplantation and post-Liver transplantation. DAA: Direct-acting antiviral.
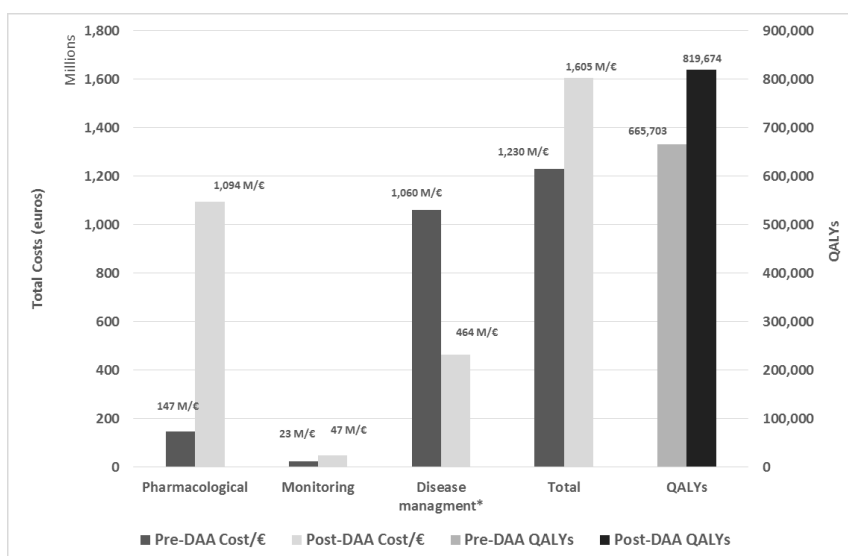

Fig. 1. Results of the analysis of the 51,900 patient cohort with the post-DAA strategy compared to the pre-DAA strategy, a discount rate of 3% was applied to health costs

and outcome (*costs of disease management -fibrosis, cirrhosis, SVR, regression of liver cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplantation. Incremental cost post-DAA vs. Pre-DAA: €375 million. Incremental QALYs post-DAA vs. DAA: 153.970 QALYs.* DAA: Direct-acting antiviral; QALYs: quality-adjusted life year).

A Decompensated cirrhosis

B Hepatocellular carcinoma

C Liver transplantation

D Liver-related deaths

Fig. 2. *The annual impact on the number of clinical events with the post-DAA vs pre-DAA strategy in the analysis population, during the 50 year simulation without applying a discount rate.*

A Pre-DAA strategy

	SVR*	CC*	DC*	HCC*	LT + post-LT*	Liver-related death†	Death from the other causes†
10 years	5,476	33,266	3,140	1,300	527	6,040	2,151
20 years	4,801	19,724	2,898	1,057	1,022	16,371	6,027
30 years	3,460	8,811	1,600	553	877	23,972	12,627
40 years	1,169	1,687	345	116	269	27,213	21,101
50 years	78	55	12	4	13	27,659	24,078

B Post-DAA strategy

	SVR*	CC*	DC*	HCC*	LT + post-LT*	Liver-related death†	Death from the other causes†
10 years	33,677	11,181	1,193	612	233	2,795	2,208
20 years	29,532	6,617	1,045	459	420	7,075	6,752
30 years	21,285	2,954	563	239	348	10,086	16,425
40 years	7,192	566	120	53	105	11,366	32,498
50 years	479	19	4	2	5	11,547	39,844

Fig. 3. *The evolution (or progression) of the disease of pre-DAA and post-DAA, without applying the discount rate (*Number of patients in a particular health state during years 10, 20, 30, 40 and 50. †Accumulated patients from year 0 to 10, 20, 30, 40 and 50. DC: Decompensated cirrhosis; HCC: Hepatocellular carcinoma; LT: Liver transplantation; Post-LT: Post-liver transplantation; Regr. HC: Regression of liver cirrhosis).*
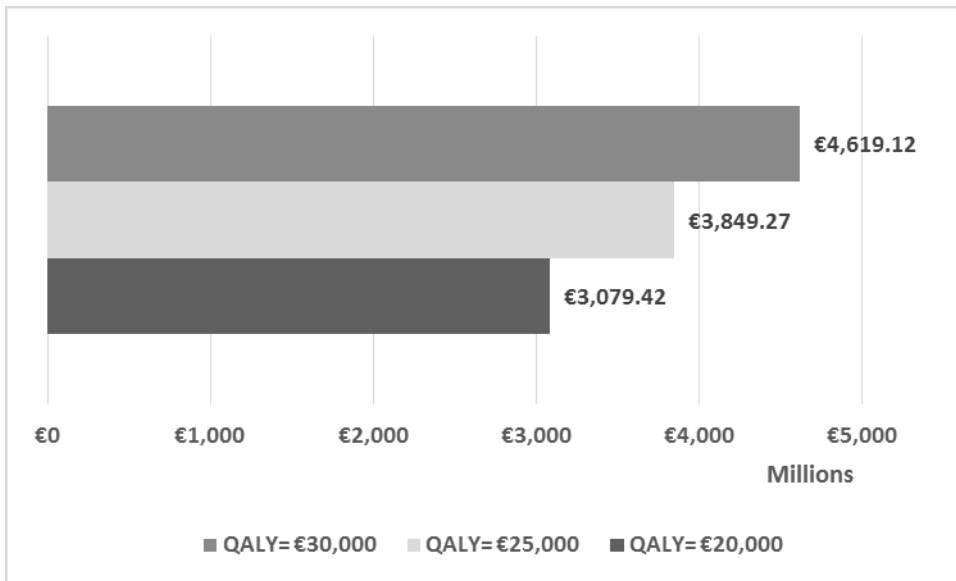
Fig. 4. *Estimates of the monetary value according to different values of cost per QALYs obtained with the post-DAA strategy* vs. *the pre-DAA strategy (estimates of the monetary value obtained with the post-DAA strategy* vs. *the pre-DAA strategy in the study population according to different cost values per QALYs (€20,000, €25,000 and €30,000), compared to the results of the analysis when applying a discount rate of 3% for costs and outcome.* QALY: quality-adjusted life year).