Master's Degree Dissertation

Cost-effectiveness and cost-utility study of hypercholesterolemia treatment in Spain: Evolocumab added to Standard of Care vs Standard of Care.

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Resumen

Antecedentes. Las enfermedades cardiovasculares suponen una importante carga económica para los sistemas sanitarios. Existen tratamientos eficaces para la hipercolesterolemia, siendo las estatinas el estándar de tratamiento actual. Un inhibidor de la PCSK9, evolocumab, también ha demostrado su eficacia para reducir los eventos cardiovasculares en estos pacientes. Este estudio evalúa el coste-efectividad y coste-utilidad de evolocumab frente al tratamiento estándar desde la perspectiva del Sistema Nacional de Salud (SNS).

Métodos. Se desarrolló un modelo de Markov a 20 años, basado en una cadena de Markov que incluye estimaciones de efectividad, años de vida libres de progresión, años de vida ajustados por calidad y costes. Se utilizaron ciclos mensuales para ajustar el curso de la enfermedad. Las medidas de resultado fueron los eventos cardiovasculares evitados, los años de vida y los años de vida ajustados por calidad (AVAC). Por último, se empleó una simulación de Monte Carlo para gestionar la incertidumbre y se presentó una curva de aceptabilidad.

Resultados. Los ratios de coste-efectividad incremental y de coste de utilidad incremental por paciente obtenidos fueron 59.895,20 € por año de vida libre de progresión y 289.677,66 € por AVAC ganado, respectivamente. Los ratios obtenidos para el estándar de atención y para evolocumab añadido al estándar de atención en ese orden fueron de 191,73 € y 7.238,04 € por año de vida libre de progresión y 141,04 € y 5.916,71 € por año de vida ajustado por calidad ganado.

Conclusiones. A la luz de estos resultados, y asumiendo un umbral de referencia de 30.000 euros/QALY para el SNS, añadir evolocumab al tratamiento estándar no es rentable en comparación con el tratamiento estándar solo. Sin embargo, estos resultados deben interpretarse con precaución, ya que evolocumab puede seguir siendo rentable en algunos subgrupos específicos de pacientes. Aunque en España no se utiliza un umbral de coste-efectividad explícito para decidir los niveles de financiación y/o precios, este trabajo puede contribuir a informar la toma de decisiones en nuestro entorno.

Keywords: hipercolesterolemia, evolocumab, coste-efectividad, coste-utilidad, AVAC, Markov, sistema nacional de salud

Abstract

Background. Cardiovascular diseases have a significant economic burden on healthcare systems. Effective treatments for hypercholesterolemia are available, with statins being currently the standard of care. A PCSK9 inhibitor, evolocumab, has also shown efficacy in reducing cardiovascular events in these patients. This study evaluates the cost-effectiveness and cost-utility of evolocumab with standard of care vs standard of care alone from the perspective of the Spanish National Health System (sNHS).

Methods. A 20 years Markov model, based on a Markov chain developed including estimates of effectiveness, progression-free life years, quality-adjusted life years and costs. Monthly cycles were used to fit the disease course. Outcome measures were avoided cardiovascular events, life years and quality-adjusted life years (QALYs). Finally, a Monte Carlo simulation to manage uncertainty was employed and an acceptability curve was presented.

Results. The incremental cost-effectiveness and incremental utility cost ratios per patient obtained were 59.895,20 € per life year free of progression and 289.677,66 € per QALY gained, respectively. The ratios obtained for the standard of care and for evolocumab added to the standard of care in that order were 191.73€ and 7,238.04€ per progression-free life year and 141.04€ and 5,916.71€ per quality-adjusted life year gained.

Conclusions. In light of these results, and assuming a reference threshold of €30,000/QALY for the sNHS, adding evolocumab to standard treatment is not cost- effective when compared to standard treatment alone. However, these results should be interpreted with caution, as evolocumab may still provide cost-effective value in some specific subgroups of patients. Even if no explicit cost-effectiveness threshold is used in Spain to decide funding and/or pricing levels, this work may contribute to inform decision-making in our setting.

Keywords: hypercholesterolemia, evolocumab, cost-effectiveness, cost-utility, QALY, Markov, national health system

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INTRODUCTION

Cardiovascular diseases of which ASCVD (Atherosclerotic cardiovascular disease) is the major component, is responsible for >4 million deaths in Europe each year.[1] In Spain, the relevance of cardiovascular diseases is due to their high mortality (35% of all deaths, causing nearly 125,000 each year) and morbidity (more than 560,000 patients discharged and five million hospital stays per year), the high prevalence of their main risk factors in the Spanish population and their high socioeconomic impact as cardiovascular disease care is responsible for 15% of total healthcare costs.[2]

Hypercholesterolemia (HC) is one of the main cardiovascular risk factors, especially associated with the development of ischemic heart disease. HC is defined as the presence of cholesterol in the blood above the levels considered normal. Normal total cholesterol levels are situated at <200mg/dl, considering that cholesterol between 200 and 240 mg/dl is a normal level; 200 and 240 mg/dl is a normal-high level and above 240mg/dl is a high level.[3] In addition, according to the National Health Survey (2017) 18% of the Spanish population suffers from hypercholesterolemia.

There are not many studies assessing the economic impact of hypercholesterolemia and its relationship with the cardiovascular diseases but according to the WHO, high cholesterol is the fourth most important health threat measured in Disability-Adjusted Life-Years in Europe and hypercholesterolemia is the fifth largest contributor to healthcare costs in the EU and the sixth largest in terms of productivity costs.[4]

Statistics from the European Heart Network (EHN) in its 2017 edition estimate that cardiovascular disease (CVD) costs the EU economy €210 billion per year. Of the total cost of CVD in the EU, around 53% (€111 billion) is due to healthcare costs, 26% (€54 billion) to productivity losses and 21% (€45 billion) to informal care for people with one of these conditions [4] and in Spain, cardiovascular diseases are estimated to cost 9 billion euros annually[5].

As explained above, it seems that lowering cholesterol levels would lead to a reduction in cardiovascular disease rates and therefore have a major economic impact. In addition to lifestyle modifications, which is the first line of therapeutic approach in most countries. The second therapeutic line are pharmacological treatments available to reduce blood cholesterol levels.

Most of the therapeutic and management guidelines for hypercholesterolemia state that the first step in hypercholesterolemia treatment is diet and exercising, but this measure is usually not enough to reach acceptable cholesterol levels. In this case, the standard of care is the administration of different type of statins in monotherapy or combined with ezetimibe and/or resins if the patient is still uncontrolled. However, there remain patients who, despite the listed interventions, are still unable to control their cholesterol levels with the resulting cardiovascular risk. The European Medicines Agency approved in 2015 a treatment called evolocumab (Repatha®), a PCSK9 inhibitor that has demonstrated efficacy in reducing LDL-cholesterol levels when is added to statins and/or other

treatments for high cholesterol levels such as ezetimibe, and it has recently shown a significant reduction of cardiovascular events as a consequence of the former. [6,7,8,9,10]

In Spain, evolocumab is funded for the following indications along with maximum tolerated doses of statins: uncontrolled established cardiovascular disease (ischemic heart disease, ischemic cerebrovascular disease and peripheral arterial disease), uncontrolled homozygous familial hypercholesterolemia, patients with uncontrolled heterozygous familial hypercholesterolemia and only for any of the patients in the above groups who are intolerant to statins or in whom statins are contraindicated and whose c-ldl is greater than 100 mg/dl.[11]

Due to the high price associated to this new treatment, this study evaluates the cost-effectiveness and cost-utility of evolocumab in addition to standard of care vs standard of care, taking into account not only effectiveness and cost data but also quality of life data as it is gaining more and more importance in pharmacoeconomic studies, allowing patients' preferences to be incorporated in decision making[12].

METHODS AND MATERIALS

This study is a cost-effectiveness and cost-utility analysis to evaluate the standard of care (SoC) versus evolocumab plus standard of care (Evo +SoC) for the management of hypercholesterolemia based on the positive results obtained regarding cardiovascular disease when managing high blood cholesterol levels. The standard of care for hypercholesterolemia treatment in Spain is based on statins at high dose, as mentioned before in the introduction.[6,7] This assessment was based on the calculation of the incremental cost-effectiveness ratio and incremental cost-utility ratio. For the former the model used as the effectiveness measure the life years free of progression, which refers to the time that elapses without an individual developing cardiovascular events including cardiovascular death, myocardial infarction, stroke, hospitalization due to unstable angina, or coronary revascularization. In the case of the later, the measure used to calculate the quality of life is quality adjusted life years gained. The perspective for this study is the Spanish National Health System (sNHS). A Markov model composed of two mutually exclusive states, progression-free and new cardiovascular event, was built in Excel following the Markov chain structure since the probabilities remained constant over time. [7]

Based on Olry de Labry's et al study, one-month cycles were established. The outcomes taken into account for this study were the primary effectiveness measure included in the study previously mentioned, which was the rate of cardiovascular events avoided in 26 months, 11,3% for standard of care and 9,8% for evolocumab plus standard of care, which had been transformed into transition probabilities by the formula $P= 1-e^{-rt}$, where *r* corresponds to the rate and *t* to the time. The final transitions obtained were 0,00376 and 0,00510 for evolocumab plus SoC and SoC, respectively. The effectiveness outcomes came in turn from the FOURIER study, that reflected the time to the occurrence of a cardiovascular event in patients with moderate- or high-intensity statins and at least one additional cardiovascular treatment to whom evolocumab or placebo was administered (progression-free life

years). The FOURIER study was carried out in 49 countries and two effectiveness measures were obtained, the primary: the composite of cardiovascular death, myocardial infarction, stroke, hospitalization due to unstable angina, or coronary revascularization, and secondary: the composite of cardiovascular death, myocardial infarction, or stroke. In this study only considers the primary as mentioned at the beginning. [6]

QALYs were calculated based on the average time a patient spends in each health state and the utility associated to each health condition. For a cohort of 1000 patients, the number of patients in each health state was calculated from the transition probability and the proportion of patients in each state related also to the parameters described in Olry de Labry's et al study from the FOURIER study. The utilities used for this model were the ones included in Stam-Slob MC et al. study.[14] These utilities were assigned for the Netherlands population but for the purpose of the study it was assumed that the characteristics of the Netherlands and the Spanish population were similar enough. Furthermore, the utilities related to any kind of death were assumed to be 0, and it was also assumed that those associated with myocardial infarction and coronary revascularization were the same based on the information available. The no cardiovascular disease health state utility was estimated as 0.891 for the Spanish population older than 65 years.[13] Direct health costs and costs related to cardiovascular complications arisen from hypercholesterolemia were measured in euros and are also gathered from Olry de Labry's et al study. [7] Indirect costs caused by the loss of productivity associated with the occurrence of cardiovascular events during the individual's lifetime were excluded because of the perspective of the study.

Given that the mean age of the patients enrolled in the FOURIER study was 62.5 years and the mean life expectancy in Spain in 2020 was 82.34, a time horizon of 20 years was proposed for the model.[15] Since the period of time was several years from the baseline, an annual discount rate of 3.0% to correct them was applied to both outcomes and costs.[16] In order to adjust this percentage to a monthly basis, the final discount applied was 0,25%.

A probabilistic sensitivity analysis was performed through a Monte Carlo simulation with 1000 iterations to manage uncertainty. Its results were reflected in a cost-effectiveness plane and an acceptability curve. In order to obtain the later, the net monetary benefit and then the alternative that had the great benefit for each iteration had been calculated and then represented in graphs. For this analysis, the distributions applied to the different parameters introduced in the model were beta for all the efficacy measures, gamma distribution for the costs, 1-gamma for the utilities and uniform in the case of the discount rates.

There is some controversy regarding the acceptability threshold for Spain, since there is not an official one to be considered. According to the literature review, most of the economic evaluation studies set this threshold in 30000 €/ QALYs, therefore, it is the one established here, although there are others who set it at 45,000 €/ QALY or speak of a double threshold. [17,18,19]

All this data and sources are summarized in table 1 of the annex.

RESULTS

Regarding the results shown after performing a total of 240 monthly cycles, the cost of statins and evolocumab plus statins over the 20-year period together with the resulting cost of associated cardiovascular events for the two cases during are 1976,50€ and 84600,84 €, respectively. This increase in costs is accompanied by another increase in life years free of progression and in quality adjusted life-years, but not of the same magnitude. The resulting life years free of progression per patient are 10,30 for standard of care versus 11,68 for evolocumab plus standard of care and the resulting utility for the whole period per patient is 14,01 and 14,29 QALYs.

The Markov chain final results are shown in Table 2 attached at the annex.

The multivariate probabilistic sensitivity analysis confirmed model robustness and reduced the effect of uncertainty. After running in Excel the Monte Carlo simulation, as it was a simple model, 1000 iterations were obtained. The results of this analysis were consistent with the ones obtained in the deterministic model. The average costs obtained were 84.856,30 € for Evo + SoC and 1.983,12€ for SoC. With regards to efficacy measures the average life year free of progression per patient obtained were 11,77 and 10,37, respectively. Finally, the average QALYs per patient obtained after running the simulation were 14,41 and 14,12 in that order. If we compare these results with the ones obtained in the deterministic model we can see they were quite similar. The results of one of the simulations carried out are listed on the table 3 of the annex. To illustrate the simulation, a cost-effectiveness (Figure 1) and an acceptability curve (Figure 2) graphs have been also attached at the annex.

DISCUSSION

An economic model to determine the cost-effectiveness of the recently approved treatment evolocumab in Spanish population for the treatment of hypercholesterolemia aiming to reduce the cardiovascular events arisen from the high cholesterol levels was developed, using as outcomes measures the cost per progression-free life year and cost per QALY gained. With regard to quality-adjusted life years, the incremental cost-utility ratio obtained was 289.677,66€ per quality adjusted life year gained per patient. In this case we do have a reference on the acceptable threshold for Spain in terms of gains in quality-adjusted life years and for this study we have considered 30.000€ per quality-adjusted life year gained. In light of these results, evolocumab as an add-on to statins is not cost-effective compared to statins alone. The difference in the rate of cardiovascular events avoided for both treatments was not high enough to justify the incremental cost needed to afford the PCSK9 inhibitor. If we consider other scenarios, such as increasing the threshold to €45.000/QALY as in other studies, evolocumab would still not be the option of choice. On the other hand, if we look at the thresholds set as a reference for other countries with population characteristics close to Spain such as the Netherlands or the United Kingdom, we find values of 20000-80.000€/QALY and 23.367-35.050€/QALY [19], therefore, it would not be cost-effective for the national health system of these countries either. At this point, it is necessary to point out that this model included all patients susceptible to treatment for hypercholesterolemia regardless of their characteristics but the literature reviewed

showed that in some cases evolocumab plus standard of care could be cost-effective for certain subgroups of patients.

Regarding progression-free life years, the incremental cost-effectiveness ratio obtained was 59.895,20 € per life year free of progression for each patient. Even if there is no reference in the literature about what could be acceptable to pay to gain one year free of progression, our results may be informative in terms of budgetary healthcare decision-making within the sNHS , as they provide relative cost and effectiveness estimates.

However, based on these considerations and our findings, it seems reasonable to keep evolocumab therapy in the sNHS when statins are not sufficient to control blood cholesterol levels with standard treatment or for those who cannot tolerate it. Also, a price reduction of evolocumab has been proposed (Olry de Labry`s et all), to reduce its ICER. In the context of the sNHS, the key question is whether there is the ability and the determination to implement a payment model based on value, that improves the predictability, consistency and transparency of the process for all the stakeholders involved (regulatory agencies, payers, pharmaceutical and medical devices industry, healthcare managers and professionals, and patients) and that allows for an efficient and orderly allocation of public resources.

This study has some limitations. First, the disease course has been simplified compared to other studies reviewed. The disease is, in fact, more complex that what it has been described here, the patient could develop more than one cardiovascular event during his/her life and could transition between cardiovascular events, may suffer more than one cardiovascular event and of different types during the course of the disease. Second, our results reflect cost-utility for a reference population that includes patients with very different risk levels (primary and secondary prevention, different type of cholesterolemia or base blood cholesterol levels) [8,9,10,15,14,20]. In this way, these results should be interpreted with caution, as evolocumab may still provide cost-effective value in specific subgroups of patients, such as patients intolerant to statins or severe patients that improve when using the drug as an add-on to statins at maximum dose. Third, the target population of this study is the Spanish population, while the measures of effectiveness belong to the FOURIER study, which was carried out in 49 different countries, and the utilities applied to calculate the quality of life associated to each health state belong to the Netherlands population. Population differences could affect the final results in effectiveness. Fourth, , the secondary measure of effectiveness collected in the FOURIER study and consequently in Olry de Labry's et al. have not been taken into account in this analysis for model simplification purposes. Fifth, the FOURIER study evaluates efficacy at 26 months, but it does not take into account the development of the disease during the patient's lifetime (which is, approximately, the time period considered in this study), nor other associated causes that could be triggers for cholesterol reduction., Long-term effectiveness and safety measures are needed and would have provided more reliable estimates. Sixth, use of ezetimibe was not included in this study (5% of patients in the FOURIER study were treated with ezetimibe), resulting in a slight infraestimation of costs.. Finally, indirect costs have not been

included in this study, and the existing evidence shows loss of productivity costs or caregivers costs may be important in ischemic diseases. [21]

After this analysis, it can be concluded that based on the information currently available, evolocumab added to statins is not cost-effective compared to statin monotherapy, neither in terms of effectiveness nor quality of life. However, it is necessary to be cautious, since it could be a cost-effective alternative for certain subgroups of patients, which would be interesting to evaluate in future studies.The results shown in this study could be useful for information purposes when making decisions on the financing or use of drugs by the sNHS. There is growing evidence that it would be worthwhile to move towards a value-based, predictable, consistent and legitimate system of technology incorporation that would allow clear and detailed funding and indication decisions to be made in situations such as this one.

ANNEX

TABLE 1. MODEL INPUTS

	Value	Reference
Efficacy Parameters		
Probability of having a cardiovascular event (monthly)		
evolocumab + SoC*	0,00376	Olry de Labry's et al [7] 2018
SoC	0,00510	Olry de Labry's et al [7] 2018
Proportion of events		
Cardiovascular death	0,1294	Olry de Labry's et al [7] 2018
Myocardial infarction	0,2446	Olry de Labry's et al [7] 2018
Hospitalization due to unstable angina	0,1223	Olry de Labry's et al [7] 2018
Stroke	0,1079	Olry de Labry's et al [7] 2018
Coronary revascularization	0,3956	Olry de Labry's et al [7] 2018
Cost Parameters (monthly)		
SoC	8,73	Olry de Labry's et al [7] 2018
evolocumab + SoC	422,89	Olry de Labry's et al [7] 2018
Cardiovascular death	417,85	Olry de Labry's et al [7] 2018
Myocardial infarction	326,05	Olry de Labry's et al [7] 2018
Hospitalization due to unstable angina	230,47	Olry de Labry's et al [7] 2018
Stroke	416,21	Olry de Labry's et al [7] 2018
Coronary revascularization	493,73	Olry de Labry's et al [7] 2018
Utilities		
Cardiovascular death	0	*Assumed*
Myocardial infarction	0,79	Stam-Slob MC et al.[14] study 2018
Hospitalization due to unstable angina	0,78	Stam-Slob MC et al.[14] study 2018
Stroke	0,77	Stam-Slob MC et al.[14] study 2018
Coronary revascularization	0,79	Stam-Slob MC et al.[14] study 2018
Progression Free	0,891	Szende A et al. [13] 2014

*SoC: Standard of Care

TABLE 2. MARKOV MODEL RESULTS

	SoC*	Evo + SoC*	Difference
LIFE YEARS FREE OF PROGRESSION	10,31	11,69	**1,38**
QALYs	14,01	14,30	**0,29**
COSTS (€)	1.976,50	84.600,84	**82.624,34**
Incremental Cost-Effectiveness Ratio (€/Progression-free life year)	191,73	7.238,04	**59.895,20**
Incremental Cost-Utility Ratio (€/QALYs)	141,04	5.916,71	**289.677,66**

SoC: Standard of Care; Evo+SoC: evolocumab + Standard of Care

TABLE 3. RESULTS OBTAINED AFTER RUNNING MONTE CARLO SIMULATION IN EXCEL [a]

	pCVE_Evo	pCVE_StdTh	CVDth_prop	MI_prop	Hospi_prop	Stroke_prop	CR_prop	StTreat_cost	Evo_Statins_cost	CVDth_cost	MI_cost	Hospi_cost	Stroke_cost	CR_cost
Simulation	0,00376	0,00510	0,13	0,24	0,12	0,11	0,40	416,21	422,89	417,85	326,05	230,47	416,21	493,73
Average	0,00376	0,00510	0,13	0,24	0,12	0,11	0,40	414,61	423,24	419,15	325,65	230,51	414,61	494,37
Deviation	0,00018	0,00025	0,01	0,01	0,01	0,01	0,02	21,04	21,36	20,79	16,12	11,46	21,04	25,16
Minimum	0,00323	0,00426	0,11	0,21	0,10	0,09	0,34	346,86	345,21	356,04	284,63	195,19	346,86	420,64
Maximum	0,00436	0,00587	0,15	0,30	0,14	0,13	0,47	486,59	504,51	486,92	380,22	268,80	486,59	598,22

	U_CVDth	U_MI	U_Hospi	U_Stroke	U_CR	U_Pfree	Discount_benef	Discount_cost
Simulation	-	0,79	0,78	0,77	0,79	0,89	0,0025	0,0025
Average	-	0,79	0,78	0,77	0,79	0,89	0,0024	0,0025
Deviation	-	0,04	0,04	0,04	0,04	0,04	0,0014	0,0014
Minimum	-	0,64	0,65	0,61	0,64	0,68	0,0000	0,0000
Maximum	-	0,88	0,88	0,90	0,89	0,97	0,0050	0,0050

	SoC LyearPF	SoC QALYs	SoC costs	Evo LyearPF	Evo QALYs	Evo costs	Incremental QALYs	Incremental LYPFree	Incremental cost	ICER (QALY)	ICER (LYG)
Simulation	10,31	14,01	1.976,50	11,69	14,30	84.600,84	0,29	1,38	82.624,34	289.677,66	59.895,20
Average	10,37	14,12	1.983,12	11,77	14,41	84.856,30	0,29	1,40	82.873,18	368.591,82	63.311,25
Deviation	0,71	1,23	175,62	0,83	1,28	7.837,67	0,11	0,34	7.710,07	599.913,57	19.068,09
Minimum	8,72	11,12	1.574,96	9,95	11,19	63.660,96	-0,04	0,39	61.769,58	2.016.675,55	29.426,81
Maximum	12,07	16,97	2.484,10	13,65	17,46	108.400,68	0,77	2,60	106.181,22	14.602.689,62	194.866,21

a. ***References: pCVE_Evo: probability of cardiovascular event with Evo + SoC; pCVE_StdTh: probability of cardiovascular event with SoC; CVDth_prop: proportion of cardiovascular death; MI_prop: proportion of Myocardial Infarction; Hospi_pro: proportion of*** hospitalization due to unstable angina***; Stroke_pro: proportion of stroke; CR_prop: proportion of coronary revascularization; StTreat_cost: Cost of SoC; Evo_Statins_cost: cost of Evo+SoC; CVDth_cost: cost of an individual suffering cardiovascular death; MI_cost; cost of an individual suffering myocardial infarction; Hospi_cost: cost of an individual suffering hospitalization due unstable angina; Stroke_cost: cost of an individual suffering stroke; CR_cost: cost of an individual suffering coronary revascularization; U_CVDth: utility associated to cardiovascular death; U_MI: utility associated to myocardial infarction; U_Hospi: utility associated to hospitalization due unstable angina; U_Stroke: utility associated to stroke; U_CR: utility associated to coronary revascularization; U_Pfree: utility associated to no event; LyearPF:L ife years free of progression***

FIGURE 1. COST-EFFECTIVENESS PLANE FOR STANDARD OF CARE VS EVOLOCUMAB PLUS STANDARD OF CARE.

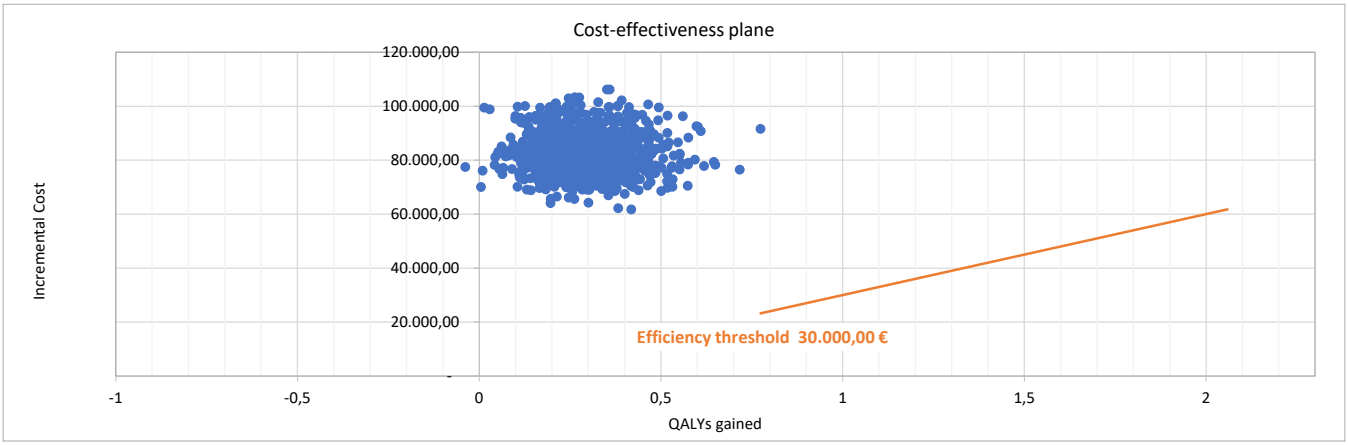
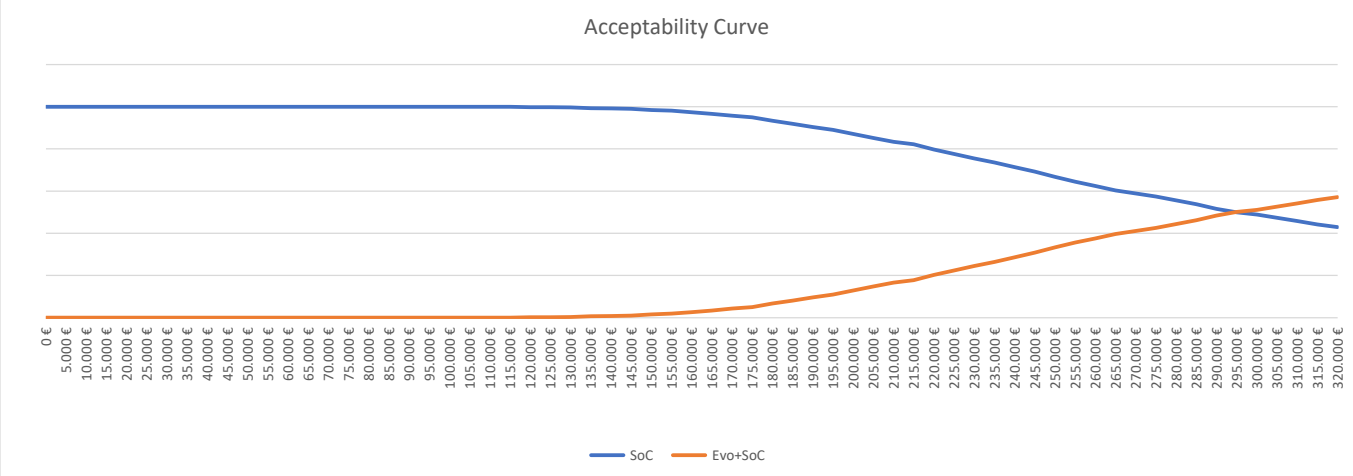


FIGURE 2. ACCEPTABILITY CURVE FOR STANDARD OF CARE VS EVOLOCUMAB PLUS STANDARD OF CARE



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