



# Economic evaluation of evolocumab in uncontrolled patients with high-risk cardiovascular disease affected by primary hypercholesterolemia and mixed dyslipidemia

*Evaluación económica de evolocumab en pacientes con enfermedad cardiovascular de alto riesgo con hipercolesterolemia primaria y dislipidemia mixta no controlados*

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## Keywords:

Economic evaluation, cost-effectiveness, economic impact, evolocumab, cardiovascular disease, hypercholesterolemia.

## Palabras clave:

Evaluación económica, costo-efectividad, impacto económico, evolocumab, enfermedad cardiovascular, hipercolesterolemia.

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## ABSTRACT

**Introduction:** Cardiovascular diseases (CVDs) are the leading cause of death worldwide, imposing an enormous clinical and financial burden on healthcare systems. An elevated level of low-density lipoprotein cholesterol (LDL-C) constitutes one of the most important modifiable risk factors for CVDs. **Objectives:** To assess the economic and health outcomes of evolocumab (EVO) added to standard of care (SoC, high-intensity statin with/without ezetimibe) in uncontrolled high-risk adult patients with primary hypercholesterolemia and mixed dyslipidemia (PHMD) in the Mexican Institute of Social Security. **Material and methods:** Using a lifetime Markov model comprising seven health states with annual cycles, we compared the direct medical costs (acquisition of lipid-lowering therapies besides the costs associated with each health state and costs for a transitory event called revascularization), and life-years (LY) expected with EVO+SoC vs SoC alone. The target population was categorized into two groups: PHMD with a history of either myocardial infarction or ischemic stroke and heterozygous familial hypercholesterolemia (HeFH). Both future costs and LY were discounted at a 5% annual rate. **Results:** EVO+SoC had a higher acquisition cost than SoC but was also more effective. The cost per LY additionally gained by using EVO was modeled as \$348,629 (MXN) in the first subpopulation and \$298,148 (MXN) in patients with HeFH. The model remained robust to plausible changes in the parameters. The probability of EVO+SoC being cost-effective under a willingness to pay threshold of 3 times the gross domestic product per capita estimated for 2020 in Mexico was close to 100% in both subpopulations. **Conclusions:** EVO+SoC may provide a cost-effective intervention.

## RESUMEN

**Introducción:** Las enfermedades cardiovasculares (ECVs) son la principal causa de mortalidad mundial, imponiendo una enorme carga clínica/financiera a los sistemas de salud. Un nivel elevado de colesterol de lipoproteínas de baja densidad (C-LDL) constituye uno de los factores de riesgo modificables más importantes para ECVs. **Objetivos:** Evaluar desenlaces económicos y de salud de evolocumab (EVO) agregado al estándar de atención (SoC, estatina de alta intensidad con/sin ezetimiba) en adultos de alto riesgo no controlados, con hipercolesterolemia primaria y dislipidemia mixta (HPDM) en el Instituto Mexicano del Seguro Social. **Material y métodos:** Usando un modelo Markov de siete estados de salud, de por vida con ciclos anuales, comparamos costos directos (adquisición de terapias hipolipemiantes, costos según estados de salud y del evento transitorio «revascularización») y años de vida (AV) esperados con EVO+SoC vs SoC. La población objetivo se dividió en dos grupos: HPDM con antecedentes de infarto de miocardio o accidente cerebrovascular isquémico; hipercolesterolemia familiar heterocigótica (HFHe). Costos y AV futuros se descontaron 5% anualmente. **Resultados:** EVO+SoC fue más costoso y más efectivo que SoC. El costo por AV ganado por el uso de EVO fue \$348,629 (MXN) en la primera subpoblación y \$298,148 (MXN) en pacientes con HFHe. El modelo se mantuvo robusto ante cambios plausibles en los parámetros. La probabilidad de que EVO+SoC sea costo-efectivo para un umbral de aceptabilidad igual a tres veces el producto interno bruto per cápita estimado para 2020 en México fue cercana a 100% en ambas subpoblaciones. **Conclusiones:** EVO+SoC puede proveer una intervención costo-efectiva.

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### INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, taking an estimated 17.8 million lives (31.8% of all global deaths) in 2017, with coronary heart disease as well as stroke comprising 85% of the total CVD-related deaths.<sup>1</sup> In addition, CVDs constitute the top cause of disability-adjusted life years (DALYs) around the world, with an approximate loss of 366 million DALYs in 2017, which represents 14.64% of the global burden of disease.<sup>2</sup> Since 1990, CVDs have remained the leading grouped cause of death in Mexico.<sup>3</sup> Almost 150,000 people died from CVDs in Mexico in 2018, for a mortality rate of 119 per 100,000 individuals.<sup>4</sup> The crude incidence and prevalence numbers of CVDs in Mexico in 2017 were estimated at 808,600 and 7.2 million, respectively.<sup>5</sup> The financial impact of CVDs is substantial due to the high number of acute episodes in addition to their chronic stages. The annual cost for hypercholesterolemia per patient in Mexico was estimated at \$258,761 (MXN), leading to an economic burden of more than \$115,000 million (MXN) in 2016.<sup>6</sup>

Statins are the first treatment choice for primary (heterozygous-familial and non-familial) hypercholesterolemia and mixed dyslipidemia (PHMD), as well as for the reduction of low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) events.<sup>7-10</sup> However, despite the availability of statins and other lipid-

lowering therapies such as ezetimibe, used either alone or in combination, many high-risk patients fail to achieve their LDL-C goals.<sup>7,9</sup> Evolocumab, a Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor, has been evaluated in several clinical trials, showing a significant reduction of LDL-C levels in different groups of patients. Recent results indicate that LDL-C reduction with evolocumab significantly reduces the risk of CV events and is also associated with atherosclerotic plaque regression.<sup>11</sup>

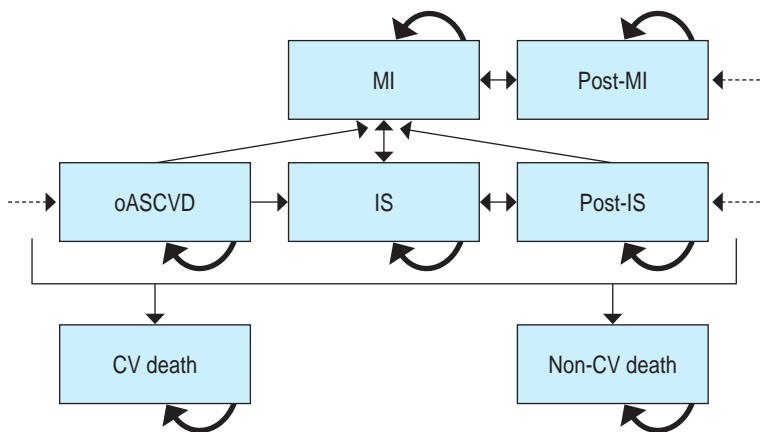
It is important to assess the economic value of evolocumab in Mexico. We used an economic model to evaluate the cost-effectiveness of evolocumab added to the standard of care of high-intensity statin therapy with or without ezetimibe (hereinafter referred to as SoC) in high-risk adult patients with PHMD with uncontrolled LDL-C levels with SoC alone from the perspective of the Mexican Institute of Social Security (IMSS).

### MATERIAL AND METHODS

A lifetime Markov cohort state-transition model, adapted from previous publications,<sup>12-15</sup> was built in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). The model comprises seven health states (Figure 1): myocardial infarction (MI); ischemic stroke (IS); other atherosclerotic CVD (oASCVD) that captures less severe CV events, namely peripheral artery disease, angina, transient ischemic attack, and carotid stenosis; post-MI; post-IS; CV death; and non-CV death. Only post-MI, post-IS, and oASCVD were considered as initial states. The states for MI and IS cover the first year period after the event, while post-event health states cover the subsequent years. Revascularization (RV), either urgent or elective, is included as a procedure (i.e., cost) and not as a separate health state because the baseline rates already incorporate the impact of RV on subsequent event rates. The model considers annual cycles and half-cycle correction. The effectiveness is reported in terms of life-years (LY).

### Target population

The target population comprises adult patients with PHMD and high CV risk who have



**Figure 1:** Model structure. CV = cardiovascular; IS = ischemic stroke; MI = myocardial infarction; oASCVD = other atherosclerotic cardiovascular disease.

not met their LDL-C goals despite receiving SoC. The patients were categorized into two distinct subpopulations: (i) individuals with PHMD plus a history of either MI or IS and (ii) individuals with heterozygous familial hypercholesterolemia (HeFH).

### Model inputs

**Baseline characteristics:** main baseline characteristics for individuals with PHMD plus a history of either MI or IS were defined according to the data available in the FOURIER trial (*Table 1*).<sup>16</sup> Baseline LDL-C in this subpopulation (175 mg/dL) corresponds to the midpoint of the range (160 to 190 mg/dL) considered as «high» in the CARMELA study.<sup>17</sup> Likewise, the main baseline characteristics for individuals with HeFH (*Table 2*) were defined according to data from the RUTHERFORD-2 trial.<sup>18</sup> Distribution among initial health states for individuals with HeFH (35.56% post-MI, 3.33% post-IS, 61.11% oASCVD) is also based on the RUTHERFORD-2 trial,<sup>18</sup> with specific values derived from Borissov et al.<sup>15</sup> Baseline LDL-C in this subpopulation (217.8 mg/dL) was estimated as the weighted average for patients

with definite/probable HeFH diagnosis off and on treatment, as reported by Benn et al.<sup>19</sup>

**Baseline risks:** the baseline CV event rates represent the rates for patients treated with SoC. The rates are adjusted by age and LDL-C level to reflect the risk in the target population, using the formula:

$$r_a = r_0 \times HR(\Delta\text{age}/\text{age}) \times RR^{\Delta\text{LDL}}$$

where  $r_a$  is the adjusted baseline rate;  $r_0$  is the baseline rate at mean age (see below);  $HR_{\text{age}}$  is the hazard ratio (HR) for age, taking a value of 1.03 from the model developed by Wilson et al.;<sup>20</sup>  $\Delta\text{age}$  is the age difference between cycle age and the mean age of the cohort from which the baseline rate was obtained; RR is the rate ratio (RR) per 1 mmol/L of LDL-C reduction (equal to 0.78, which is the RR for any major vascular event in the CTTC trial),<sup>21</sup> and  $\Delta\text{LDL}$  is the LDL-C difference in mmol/L after subtracting the mean LDL-C of the population being evaluated from the cohort LDL-C from which the baseline rate was obtained. The cohort baseline annual CV event rate for a mean age of 67 years and mean LDL-C level of 103.2 mg/dL for the PHMD with a history of

**Table 1: Main model inputs in the primary hypercholesterolemia and mixed dyslipidemia plus history of either myocardial infarction or ischemic stroke subpopulation.**

Description	Base-case value	Source
Baseline characteristics		
Mean age (years)	62.5	FOURIER trial <sup>16</sup>
Proportion of females (%)	24.6	FOURIER trial <sup>16</sup>
Mean LDL-C (mg/dL)	175.0	CARMELA study <sup>17</sup>
Concomitant use of ezetimibe (%)	5.2	FOURIER trial <sup>16</sup>
Distribution among initial health state		
Post-MI (%)	80.7	Based on the proportions of patients with a history of MI (81.1%) or of previous stroke (19.4%) in the FOURIER trial <sup>16</sup>
Post-IS (%)	19.3	
oASCVD (%)	0.0	
Baseline annual CV event rate*	10.0	Toth et al. <sup>13</sup>
Relative reduction of LDL-C with evolocumab (%)	59.0	FOURIER trial <sup>16</sup>

LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; IS = ischemic stroke; oASCVD = other atherosclerotic cardiovascular disease; CV = cardiovascular.  
\* Represents the rate per 100 patient-years under standard of care, calculated for a mean age of 67 years and mean LDL-C level of 103.2 mg/dL.

**Table 2: Main model inputs in the heterozygous familial hypercholesterolemia subpopulation.**

Description	Base-case value	Source
Baseline characteristics		
Mean age (years)	51.0	RUTHERFORD-2 trial <sup>18</sup>
Proportion of females (%)	42.2	RUTHERFORD-2 trial <sup>18</sup>
Mean LDL-C (mg/dL)	217.8	Benn et al. 2012 <sup>19</sup>
Concomitant use of ezetimibe (%)	62.0	RUTHERFORD-2 trial <sup>18</sup>
Distribution among initial health state		
Post-MI (%)	35.56	Derived from Borissov et al. <sup>15</sup> which used data collected in the RUTHERFORD-2 trial <sup>18</sup>
Post-IS (%)	3.33	
oASCVD (%)	61.11	
Baseline annual CV event rate*	7.99	Derived from Borissov et al. <sup>15</sup>
Relative reduction of LDL-C with evolocumab (%)	59.2	RUTHERFORD-2 trial <sup>18</sup>

LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; IS = ischemic stroke; oASCVD = other atherosclerotic cardiovascular disease; CV = cardiovascular.

\* Represents the rate per 100 patient-years under standard of care, calculated as  $-\text{LN}(1 - 0.55) / 10$ ; where LN is natural logarithm and 0.55 is the predicted 10-year risk for mean age of 51.16 years and mean LDL-C level of 155.46 mg/dL.

either MI or IS subpopulation is 10.0 per 100 patient-years (Table 1). These three parameters were obtained from an observational study conducted in the United Kingdom<sup>13</sup> that applied inclusion criteria similar to those used in the FOURIER trial.<sup>16</sup> The parameters for the cohort used as a reference in the HeFH subpopulation are shown in Table 2. The baseline CV event rates are further adjusted in the model once patients experience additional CV events based on the study by Wilson et al., where HRs due to two and three vascular beds involved (vs only one) were 1.35 and 1.83, respectively, and a CV event in the previous year increased the rate by 46%.<sup>20</sup> All rates were converted to risks assuming a constant rate over time (exponential survival function).<sup>14</sup>

**Non-CV mortality:** mortality from non-CVD causes was assumed to be the same as that of the IMSS adult beneficiary population. The age- and sex-specific non-CV mortality rates were estimated as the difference between the corresponding rates for all-cause and CV mortality, both calculated from the number of deaths (classified by cause) that occurred in individuals aged  $\geq 18$  years affiliated to IMSS in 2018 according to the National Institute of Statistics and Geography (INEGI)<sup>22</sup> and

the IMSS adult beneficiary population in the middle of 2018, based on the Mexican population projections elaborated by the National Population Council (CONAPO)<sup>23</sup> and the IMSS coverage of social security data found in the National Survey of Employment and Social Security (ENESS) 2017.<sup>24</sup>

**Treatment effect:** The predicted effectiveness of evolocumab on reducing CV event rates in each subpopulation is based on the relative LDL-C reduction observed with evolocumab in the FOURIER<sup>16</sup> and RUTHERFORD-2<sup>18</sup> trials. In particular, the model draws on the treatment differences between the mean percentage reduction of LDL-C levels with evolocumab administered subcutaneously once every two weeks and placebo (both on top of SoC): at week 48 in the FOURIER trial (59.0%,<sup>16</sup> applied to PHMD plus a history of either MI or IS) and at week 12 in the RUTHERFORD-2 trial (59.2%,<sup>18</sup> applied to HeFH). The absolute reductions in LDL-C levels with evolocumab were calculated as the product of the corresponding baseline LDL-C level and the relative reduction in LDL-C. Further, the absolute reductions were converted from mg/dL to mmol/L by dividing them by 38.67.<sup>12</sup> For SoC, the relative

reduction in LDL-C was set to zero because patients were assumed to be treated with SoC at baseline.<sup>14</sup>

Absolute LDL-C reductions from baseline were converted into reductions in CV events based on the relationship between LDL-C level and occurrence of CV events reported in the FOURIER trial. Specifically, the model employs the RRs per 1 mmol/L of LDL-C reduction estimated from the HRs for the key secondary endpoint, which consists of CV death, MI, or IS: 0.84 (95% confidence interval, 0.74-0.96) in the first year and 0.75 (0.66-0.85) for subsequent years.<sup>16</sup> The RR of CV events per 1 mmol/L of LDL-C reduction was defined as:

$$RR = HR^{(1/\Delta LDLc)}$$

where HR as it was previously referred, while  $\Delta LDLc$  indicates the mean LDL-C reduction in the FOURIER trial<sup>16</sup> after the imputation for missing values (1.38 mmol/L, equal to 53.4 mg/dL).<sup>25</sup> Hence, the adjusted rate of CV events for patients treated with evolocumab ( $r_{a\_EVO}$ ) is given by the following formula:<sup>14,15</sup>

$$r_{a\_EVO} = r_a * RR^{\Delta LDLc}$$

where  $r_a$  is the baseline CV rate adjusted by age and LDL-C level, calculated for SoC (see above).

It is important to note that the benefits of evolocumab regarding the reduction of LDL-C and CV events observed in the FOURIER trial<sup>16</sup> were largely consistent across major predefined subgroups related to demographic and disease characteristics, including baseline LDL-C level and baseline risk factors (e.g., previous CV events or presence of familial hypercholesterolemia). The benefits of evolocumab were also consistent across levels of intensity of statin therapy, regardless of ezetimibe use.<sup>16</sup> Therefore, the treatment effect observed in the overall trial population of FOURIER was applied across all modeled target subpopulations.

**Resource use and costs:** The model considers the direct medical costs consisting of the acquisition of hypolipemiant therapies plus the management associated with health states and RV procedures. All costs are expressed in Mexican pesos (MXN) at values as of August 2020. The list price of a 140-mg prefilled syringe of evolocumab (\$2,983.00 [MXN]) was provided by Amgen Mexico. The acquisition cost for high-intensity statins was calculated as a simple average of atorvastatin 40 and 80 mg/day,<sup>7</sup> using a price of \$11.20 (MXN) per 10-tablet pack of atorvastatin 20 mg.<sup>26</sup> The daily dose of ezetimibe was a 10 mg tablet,<sup>7</sup> with an acquisition cost (if applied) being calculated from a price of \$126.00 (MXN) per pack (each pack containing 28 tablets).<sup>27</sup> [Table 3](#) presents the estimates of costs associated

**Table 3: Costs for cardiovascular events and revascularization procedures.**

Item	DRG code	Cost
Myocardial infarction, acute care	281	\$157,844.05
Ischemic stroke, acute care	064	\$61,661.16
Non-fatal CV event, follow-up	Not applicable	\$30,343.28*
oASCVD, annual cost	Not applicable	\$30,343.28‡
Cardiovascular death	284	\$173,484.63
Revascularization	248 and 233§	\$230,395.20

DRG = diagnosis related groups at the Mexican Institute of Social Security (2018 version);<sup>28</sup> CV = cardiovascular; oASCVD = other atherosclerotic cardiovascular disease.  
 \* From Hunt et al.<sup>29</sup> This value was also used as annual cost for both the post-MI and post-IS health states.  
 ‡ Assumed to be equal to the follow-up cost of a non-fatal CV event.  
 § Weighted average. See description in text. Notes: (1) Costs based on DRG are expressed in operative-substantive level values.<sup>28</sup> (2) All costs were updated by inflation to 2020 and are expressed in Mexican pesos.



**Table 4: Predicted cardiovascular event rates, life years, and discounted costs.**

Outcomes	PHMD plus history of either MI or IS			HeFH		
	EVO+SoC	SoC	Difference	EVO+SoC	SoC	Difference
<b>MACE*</b>	<b>1.35</b>	<b>1.71</b>	<b>-0.36</b>	<b>1.73</b>	<b>2.28</b>	<b>-0.55</b>
MI	0.58	0.76	-0.18	0.82	1.14	-0.31
IS	0.14	0.18	-0.05	0.20	0.29	-0.09
CV death	0.63	0.77	-0.14	0.71	0.85	-0.15
<b>Life years</b>						
Undiscounted	12.50	9.35	3.15	18.31	12.73	5.58
Discounted	8.28	6.69	1.59	10.71	8.42	2.29
<b>Discounted costs (\$)</b>	<b>1,180,405</b>	<b>625,845</b>	<b>554,560</b>	<b>1,415,406</b>	<b>731,747</b>	<b>683,660</b>
LLT	564,395	8,772	555,623	738,120	18,893	719,227
Acute care	140,074	193,841	-53,767	149,003	228,601	-79,597
Follow-up	237,408	183,550	53,858	308,295	229,128	79,167
Revascularization	238,529	239,683	-1,154	219,988	255,125	-35,137

PHMD = primary hypercholesterolemia and mixed dyslipidemia; HeFH = heterozygous familial hypercholesterolemia; EVO = evolocumab; SoC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction; IS = ischemic stroke; CV = cardiovascular; LLT = lipid-lowering therapies.

\* Expressed as per patient rate. **Note:** Costs are expressed in Mexican pesos.

with diverse CV events and RV procedures. They were computed from the 2018 Diagnosis Related Groups (DRG) costs at the operative-substantive level in IMSS<sup>28</sup> and Hunt *et al.*<sup>29</sup> The annual cost for the health states denominated MI and IS was calculated as the sum of their corresponding acute care and follow-up costs. The cost of the transitory event named RV corresponds to the weighted average of percutaneous coronary intervention (PCI, DRG code 248) and coronary artery bypass graft surgery (CABG, DRG code 233), considering that most (88.3%) of the RV procedures correspond to PCI. This percentage was derived from the proportional distribution between ST-elevation myocardial infarction (STEMI; 73.2%) and non-ST-elevation myocardial infarction or unstable angina (NSTEMI/UA; 26.8%) reported in the RENASCA-IMSS study,<sup>30</sup> and the probabilities of PCI conditional to STEMI (91.8%) and NSTEMI/UA (87.0%) estimated from the RENASICA III study.<sup>31</sup> Conservatively, the cost for non-CV death was set to zero.

**Discount rates:** In the base-case, both costs and LY were discounted at a 5% annual rate, according to Mexican guidelines.<sup>32</sup>

**Sensitivity analyses:** Both deterministic and probabilistic sensitivity analyses were conducted to assess uncertainty surrounding the incremental cost-effectiveness ratio (ICER). Deterministic sensitivity analysis comprised the evaluation of five scenarios regarding the price of evolocumab (5% change up/down), discount rates (high/low according to Mexican guidelines<sup>32</sup>), and use of CTTC<sup>21</sup> RRs instead of those derived from the FOURIER trial,<sup>16</sup> in addition to the univariate analysis over the costs of CV events and other parameters involved in the risk estimations. Probabilistic sensitivity analysis consisted of 1000 second-order Monte Carlo simulations for each subpopulation, using the distributions recommended by Briggs *et al.*<sup>33</sup> gamma (with assumed standard errors equal to 10% of the mean values) for costs, normal for LDL-C reductions and mortality, and log-normal for the RRs of CV events per 1 mmol/L of LDL-C reduction and the HRs from Wilson *et al.*<sup>20</sup> The 95% confidence intervals were used to define the lower and upper bounds and to parameterize the probability distributions. Results of the scenario analyses are presented in a table, whereas those for the

univariate and probabilistic sensitivity analyses are summarized graphically through tornado diagrams and cost-effectiveness acceptability curves (CEAC).

## RESULTS

### Base case analyses

*Table 4* shows the predicted CV event rates per patient, LY (both undiscounted and discounted), and discounted costs disaggregated by item with each intervention for the two subpopulations analyzed. Evolocumab added to SoC decreased the lifetime rate of any major adverse CV event (MACE) by 21 and 24.1% in patients with PHMD plus a history of either MI or IS and in patients with HeFH, respectively. The highest absolute risk reductions were observed for MI, followed by CV death, while the relative reductions in risk varied from 17.5% (CV mortality in HeFH) to 30% (IS in HeFH). The benefit of adding evolocumab is reflected in a higher life expectancy, leading to gains of 3.15 LY for the first subpopulation and 5.58 LY for the second. These values represent relative improvements of 33.7% and 43.8%, respectively. The main cost driver in patients receiving evolocumab and SoC was the acquisition of hypolipemiant therapy,

accounting for around half of the total costs in both subpopulations. In the groups of SoC alone, costs owing to RV procedures contributed the most. Overall discounted costs in patients receiving evolocumab as add-on treatment nearly doubled those of the SoC alone, mainly driven by the differences in the acquisition cost of lipid-lowering therapies.

Since the addition of evolocumab to SoC was associated with both more costs and more effectiveness in comparison with SoC alone, incremental analyses were warranted (*Table 5*). The cost per LY gained with evolocumab added to SoC over SoC alone for patients with PHMD plus a history of either MI or IS was \$348,629 (MXN). The ICER was lower (i.e., more cost-effective) for the HeFH subpopulation, yielding a value of \$298,148 (MXN) per LY gained.

### Scenario analyses

*Table 5* shows the incremental values of cost and LY, as well as the ICERs, calculated for the five scenarios evaluated as part of the deterministic sensitivity analysis. All values can be compared to those obtained during the base case analyses. A relative variation of  $\pm 5\%$  in the price of evolocumab resulted in equivalent changes in ICER estimates. When the annual discount rate of 7% for both costs and LY was

**Table 5: Incremental cost-effectiveness analyses: evolocumab added to SoC vs SoC alone.**

Scenarios	PHMD plus history of MI or IS			HeFH		
	$\Delta$ Cost	$\Delta$ LY	ICER	$\Delta$ Cost	$\Delta$ LY	ICER
<b>Base-case</b>	<b>\$554,560</b>	<b>1.59</b>	<b>\$348,629</b>	<b>\$683,660</b>	<b>2.29</b>	<b>\$298,148</b>
5% increase in EVO price	\$582,237	1.59	\$366,029	\$719,364	2.29	\$313,719
5% decrease in EVO price	\$526,883	1.59	\$331,230	\$647,956	2.29	\$282,578
High discount rates*	\$474,304	1.26	\$376,837	\$560,506	1.70	\$329,364
Low discount rates <sup>‡</sup>	\$661,415	3.15	\$209,861	\$860,832	5.58	\$154,371
Use of CTTC rate ratios <sup>§</sup>	\$474,681	1.23	\$384,626	\$567,491	1.83	\$310,261

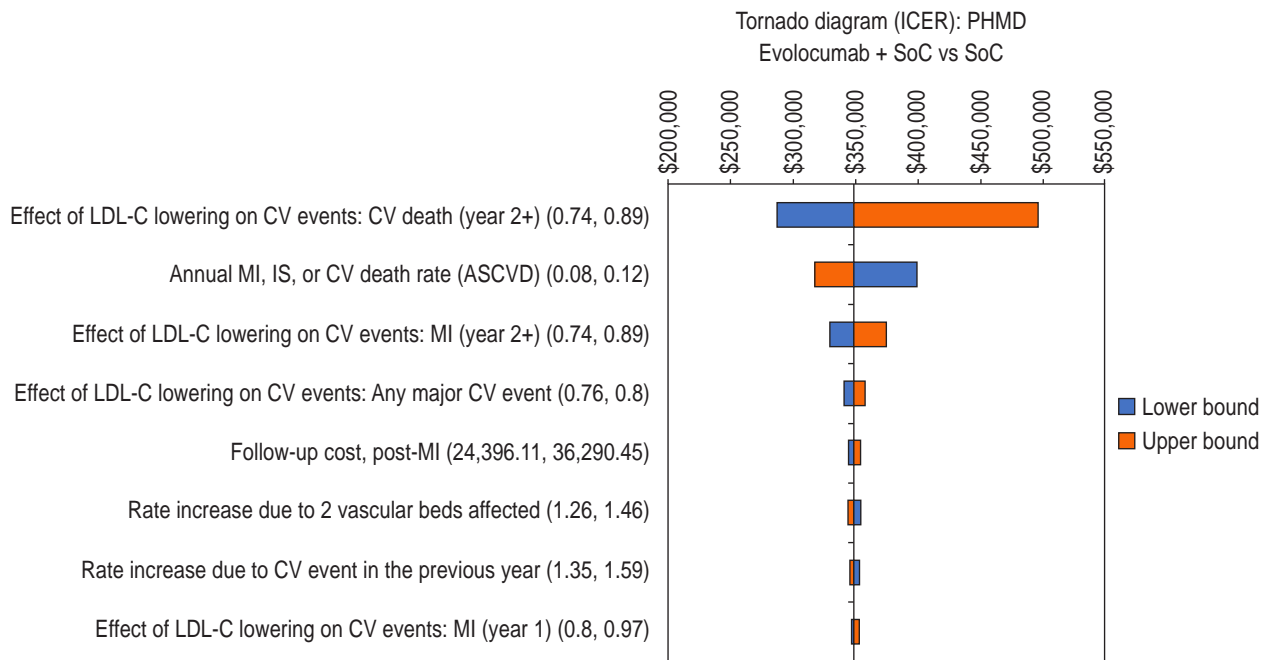
SoC = standard of care; PHMD = primary hypercholesterolemia and mixed dyslipidemia; HeFH = heterozygous familial hypercholesterolemia; LY = life years; ICER = incremental cost-effectiveness ratio; EVO = evolocumab. The symbol  $\Delta$  denotes incremental.

\* An annual rate of 7% for both costs and LY.<sup>32</sup>

<sup>‡</sup> Annual rates of 3% and 0% (i.e., undiscounted) for costs and LY,<sup>32</sup> respectively.

<sup>§</sup> 0.73 (myocardial infarction), 0.79 (ischemic stroke), and 0.86 (cardiovascular death) per 1 mmol/L of low-density lipoprotein cholesterol reduction.<sup>21</sup>

Note: All costs and ICER values are expressed in Mexican pesos.



**Figure 2:** Univariate sensitivity analyses: PHMD. Values in parentheses at the end are 95% confidence intervals. ICER values are expressed in Mexican pesos.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PHMD = primary hypercholesterolemia and mixed dyslipidemia (with a history of either MI or IS); SoC = standard of care.

applied, the ICERs increased moderately (by 8 and 10% in PHMD plus a history of either MI or IS and HeFH subpopulations, respectively). In contrast, low annual discount rates (3% for costs and 0% for LY) led to considerable improvements in ICERs, dropping their values by 40% for the PHMD with a history of either MI or IS subpopulation and 48% for the HeFH subpopulation. Using the CTTC<sup>21</sup> RRs of CV events per 1 mmol/L of LDL-C reduction instead of those derived from the FOURIER trial<sup>16</sup> produced slightly higher ICERs compared with the ones from the base case.

### Univariate sensitivity analyses

Figures 2 and 3 present the tornado diagram containing the parameters that have an impact of > 1% on the ICER for the corresponding subpopulations. In both cases, the ICER is mainly sensitive to changes in the RRs of CV events per 1 mmol/L of LDL-C reduction for CV death and MI in year two onwards and to the baseline annual MACE rate.

### Probabilistic sensitivity analyses

Figure 4 displays the CEAC with add-on evolocumab therapy for each subpopulation. The probability of evolocumab added to SoC being cost-effective compared with SoC alone under a willingness to pay threshold of \$521,435 (MXN) –which is equivalent to three times the gross domestic product (GDP) per capita for 2020 in Mexico estimated by the authors with data from the International Monetary Fund<sup>34,35</sup> available at the time the analyses were done– was 97.7% and 99.3% for PHMD plus a history of either MI or IS and HeFH subpopulations, respectively.

### DISCUSSION

To our knowledge, this is the first economic evaluation of evolocumab in Mexico. The present study found evolocumab added to SoC had ICERs of \$298,148 (MXN) in patients with HeFH and \$348,629 (MXN) in patients with PHMD plus a history of either MI or IS.

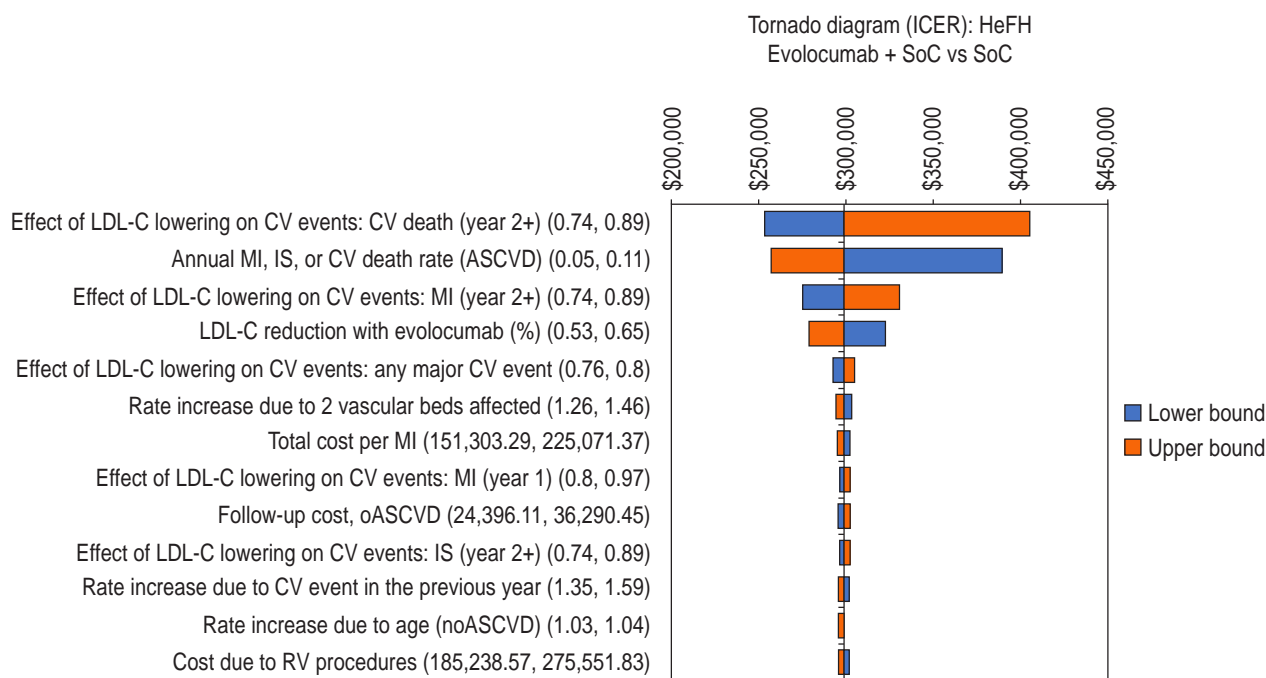


These values are equal to 1.72 and 2.00 times, respectively, our estimate of GDP per capita for 2020 in Mexico, meeting international criteria for cost-effectiveness acceptability thresholds.<sup>36</sup> Thus, despite significantly higher acquisition cost, the use of evolocumab is cost-effective due to its clinical benefit, characterized by a high potency combined with a simple dosage schedule allowing to achieve a predictable effect in LDL-C reduction, which in turn leads to a considerable decrease in risk of suffering fatal and disabling CV events. It is noteworthy that the model predicted meaningful improvements in survival for patients who received evolocumab added to SoC, yielding gains of 3.15 and 5.58 years in life expectancy over those treated with SoC alone in patients with PHMD plus a history of either MI or IS, and in patients with HeFH, respectively. Sensitivity analyses confirmed the robustness of the cost-effectiveness results.

Because of some methodological differences (e.g., health states considered, characteristics of the target population, type of prevention,

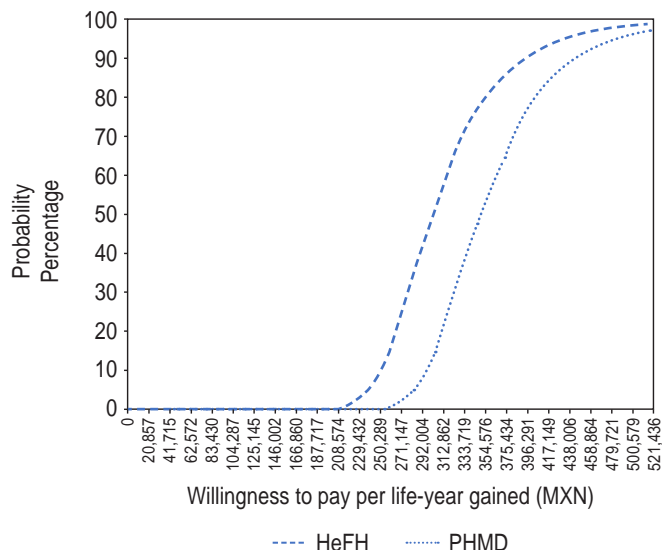
sources of clinical information, cost vectors, discount rates), it is difficult to compare the results of our study with those in other published studies. However, there is congruence in several aspects. For example, as other authors have previously reported,<sup>12-15,37-39</sup> we found that evolocumab added to SoC may provide a cost-effective intervention when administered to a certain high-risk population, such as in secondary prevention of individuals with PHMD and those with HeFH. In addition, the lower (i.e., better) ICER with HeFH predicted by our model is consistent with that in previous studies.<sup>12,14</sup>

There are several limitations to this study. First, the relative reduction in LDL-C with evolocumab applied in the model to the HeFH subpopulation is based on a short-term clinical trial.<sup>18</sup> Interestingly, the mean percentage reduction in LDL-C levels after 12 weeks of treatment in the RUTHERFORD-2 trial<sup>18</sup> (59.2%) is almost identical to the corresponding value in the FOURIER trial<sup>16</sup> (59.0%), where the



**Figure 3:** Univariate sensitivity analyses: HeFH. Values in parentheses at the end are 95% confidence intervals. ICER values are expressed in Mexican pesos.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; noASCVD = without ASCVD; oASCVD = other ASCVD; RV = revascularization; SoC = standard of care.



**Figure 4:** Cost-effectiveness acceptability curves with add-on evolocumab therapy. HeFH = heterozygous familial hypercholesterolemia; IS = ischemic stroke; MI = myocardial infarction; MXN = Mexican pesos; PHMD = primary hypercholesterolemia and mixed dyslipidemia (with a history of either MI or IS).

median duration of follow-up was 2.2 years. Second, since the model had a lifetime horizon, the effect of LDL-C lowering on CV events from year two onwards is constant, and it was based on the results of the FOURIER trial.<sup>16</sup> Although the limited follow-up time in the FOURIER trial<sup>16</sup> may have some uncertainty about the long-term effects of evolocumab. It is worth mentioning that there is evidence of sustained hypolipemiant effect with evolocumab for up to five years.<sup>40</sup> In addition, given that the process of atherosclerotic plaque accumulation and its eventual outcome in terms of CV events requires some time, it is possible to hypothesize that the therapeutic benefit of evolocumab from year three onwards will be greater in magnitude than that observed in year 2. It is also worth noting that the ICERs under the scenario considering the RRs of CV events per 1 mmol/L of LDL-C reduction found in the CTTC trial,<sup>21</sup> which had a median follow-up of 5.1 years, were similar to those obtained during the base case analyses. A third limitation is that the cost analyses were focused on certain direct medical costs. Incorporation of other sources of costs associated with CV events, such as payment of disability leave and pensions, funeral expenses, and other end-of-life costs,

would have led to more favorable results for evolocumab. Regarding this agent, its price was maintained fixed during the whole horizon but if a price erosion eventually occurred, the cost-effectiveness results would improve. Another limitation consisted of the exclusion of supplementary effectiveness measures such as the quality-adjusted life years (QALYs) or DALYs, which presumably would also lead to improved ICERs.

Finally, it is important to keep in mind that the results of these analyses are only applicable to the subpopulations evaluated, including their specific risk profiles. In the same way, the results are only generalizable to Mexican healthcare institutions with cost vectors like those of the IMSS.

### CONCLUSIONS

Results from this modeling study found that the addition of evolocumab to SoC may provide a cost-effective intervention for high-risk adult patients with PHMD plus history of either MI or IS as well as for those with HeFH when SoC alone is insufficient to meet their LDL-C goals. The cost-effectiveness of the evolocumab treatment strategy will impact longer survival and fewer complications in this type of patient at high risk of complicated CVDs.

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