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Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States

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ABSTRACT

Randomized trials have shown marked reductions in low-density lipoprotein cholesterol (LDL-C), a risk factor for cardiovascular disease (CVD), when evolocumab is administered. We hypothesized that evolocumab added to standard of care (SOC) vs SOC alone is cost-effective in the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic CVD (ASCVD) with or without statin intolerance and LDL-C >100 mg/dL. Using a Markov cohort state transition model, primary and recurrent CVD event rates were predicted considering population-specific trial-based mean risk factors and calibrated against observed rates in the real world. The LDL-C–lowering effect from population-specific phase 3 randomized studies for evolocumab was used together with estimated LDL-C–lowering effect on CVD event rates per 38.67-mg/dL LDL-C lowering from a statin-trial meta-analysis. Costs and utilities were included from published sources. Evolocumab treatment was associated with both increased cost and improved quality-adjusted life-years (QALY): HeFH (incremental cost: US$153 289, incremental QALY: 2.02, incremental cost-effectiveness ratio: US$75 863/QALY); ASCVD (US$158 307, 1.12, US$141 699/QALY); and ASCVD with statin intolerance (US$136 903, 1.36, US$100 309/QALY). Evolocumab met both the American College of Cardiology/American Heart Association (ACC/AHA) and World Health Organization (WHO) thresholds in each population evaluated. Sensitivity and scenario analyses confirmed that model results were robust to changes in model parameters. Among patients with HeFH and ASCVD with or without statin intolerance, evolocumab added to SOC may provide a cost-effective treatment option for lowering LDL-C using ACC/AHA intermediate/high value and WHO cost-effectiveness thresholds. More definitive information on the clinical and economic value of evolocumab will be available from the forthcoming CVD outcomes study.

Introduction

Approximately 86 million people in the United States have cardiovascular disease (CVD); it accounts for 1 out of every 3 deaths and remains the leading cause of death.[1] Despite the widespread use of statins, the economic burden associated with CVD is onerous, with > US$650 billion spent on CVD-related costs annually in the United States.[1,2] These costs are projected to nearly double by 2030.[1] The cost-effectiveness of new therapies has become increasingly important as healthcare costs continue to rise and information about making tradeoffs becomes critical.

Low-density lipoprotein cholesterol (LDL-C) has been established as a modifiable risk factor for CVD. A meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration (CTTC) found that every 38.67-mg/dL (1 mmol/L) reduction in LDL-C with statin therapy results in a 21% (statins vs control) and 28% (more vs less statins) reduction in rates of any major CVD event across 26 randomized trials.[3] Results from the Improved Reduction of

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Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluating ezetimibe, a cholesterol absorption inhibitor, in reducing major CVD events suggested the CTTC findings that lowering LDL-C with a nonstatin reduces the risk for a CVD event.[4]

Many high-risk patients cannot adequately reduce LDL-C levels despite intensive statin therapy. For these patients, addition of available treatment options to the standard of care (SOC) is reasonable.[5] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition has emerged as a new therapy for lowering LDL-C. The results of the phase 3 trials conducted on evolocumab, a recently approved PCSK9 inhibitor, showed that the addition of evolocumab to SOC led to average reductions in LDL-C levels of 50% to 70% in patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic CVD (ASCVD),[6,7] as well as statin intolerance.[8] A cardiovascular outcomes trial of evolocumab is ongoing (NCT01764633), but exploratory data from 2 open-label studies suggest a clinically significant reduction in cardiovascular risk with evolocumab.[9]

It is important to assess the economic value of evolocumab to payers in the United States. Economic modeling can provide US payers with information about the value of LDL-C lowering with evolocumab. We used an economic model to assess the cost-effectiveness of evolocumab added to SOC vs SOC alone in patients with hypercholesterolemia.

Methods

A Markov cohort state transition model considering a US payer perspective and a lifetime horizon and treatment duration was used to assess the cost-effectiveness of evolocumab added to SOC vs SOC alone in 3 distinct populations whose trial data are available: (1) Patients with HeFH; (2) patients with ASCVD, defined as ≥1 prior CVD event, without statin intolerance; and (3) patients with ASCVD with statin intolerance.

Each population was modeled considering patients with baseline LDL-C >100 mg/dL (Table 1). The SOC varied depending on the population: HeFH, high-intensity statins; ASCVD without statin intolerance, medium-intensity and high-intensity statins (with statin intolerance, no treatment).[5] The outcomes of the model were CVD event rates, cost per life-year (LY) gained, and cost per quality-adjusted life-year (QALY). The model was built in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA).

Model Structure

The health states included in the model (Figure 1) were no-CVD, established CVD (ECVD), acute coronary syndrome (ACS), post-ACS, ischemic stroke (IS), post-IS, heart failure (HF), post-HF, coronary heart disease (CHD) death, IS death, and non-CVD death. The CVD events included under EVCD were transient ischemic attack, peripheral vascular disease, stable angina, carotid stenosis, revascularization in the absence of myocardial infarction (MI), and abdominal aortic aneurysm. Acute coronary syndrome included MI and unstable angina. Patients could enter the model at no-CVD or at dedicated prior-CVD health states such as post-ACS, post-IS, post-HF, or ECVD. Revascularization was included as a procedure, not as a separate health-state, and the costs of revascularization were included for a proportion of patients in the ECVD, ACS, and post-ACS health states according to published data.[10,11]

Combined health states (see Supporting Information, Table 1, in the online version of this article) were created to retain memory of prior events in the model. The following assumptions for combined health states' costs, utilities, and

Table 1. Patient Demographics and Baseline Characteristics by Population

	HeFH, n = 324	ASCVD, n = 351	ASCVD (Statin-Intolerant), n = 115
Age, mean, y	51.2	62.1	64.0
Female sex, % patients	42	34	37
BMI, kg/m²	28.0	29.5	28.4
BMI <20 kg/m²	2	0	2
Type 2 DM[a], % patients	26	26	26
LDL-C, mean, mg/dL	156.5	141.3	189.4
HDL-C, mean, mg/dL	51.2	50.7	50.7
TG, mean, mg/dL	125.7	155.9	169.5
Therapy for HTN % patients	33	62	77
SBP, mm Hg	125.8	129.6	133.6
Secondary prevention % patients	39	100	100
No. of vascular beds[b], mean	1.2120	1.2120	1.2120
AF[b], % patients	11.7	11.7	11.7
Smoking, % patients	16	12	6
ASA use at baseline, % patients	39	55	69
Proportion of secondary prevention, % patients	39	100	100
10-year risk of ≥1 CVD event %	58	44	43
Initial health state[c], % patients			
ECVD	61	47	54
Post-ACS	26	29	32
Post-IS	2	5	7
Post-HF	1	8	2
Combination health states	11	15	5

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; ECVD, established cardiovascular disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HF, heart failure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.
[a]Imputed as 25.9% based on real-world US claims data,[23] because the evolocumab clinical studies had a much lower proportion of patients with type 2 DM than the US population. [b]Imputed for all populations based on Wilson et al[13] because data were not available in the study databases. [c]Percentages may not add up to 100% due to rounding.

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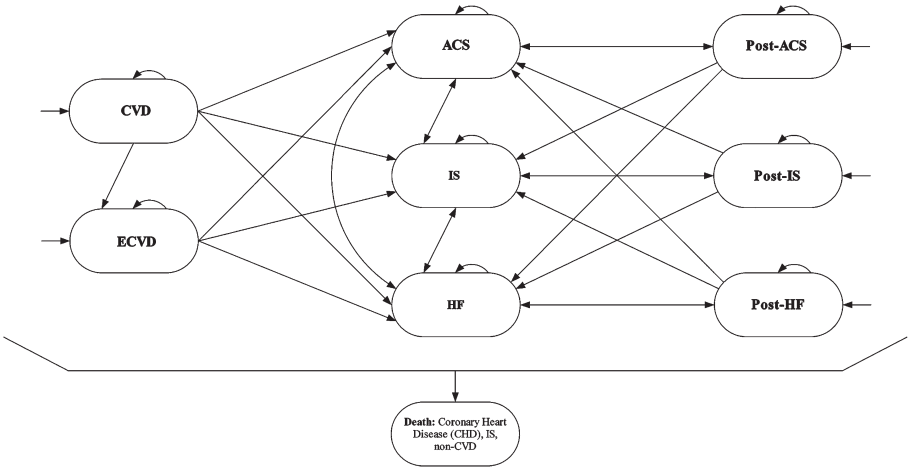

Figure 1. Evolocumab economic model structure. Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischemic stroke.

risks were considered: the highest of the costs for the individual health states involved was used as the cost for a combined health state. The costs were not added up, because addition may overestimate the costs. The lowest utility of the individual health states was used as the utility of a combined health state. The highest risk from the individual health states to a specific event was used as the risk of the combined health state to that specific event.

Model Inputs

Baseline Risks: Published risk-prediction engines[12,13] for primary (Framingham) and recurrent (Reduction of Atherothrombosis for Continued Health [REACH]) CVD events for SOC alone, calibrated using rate ratios to reflect real-world scenarios, were used to estimate the baseline CVD risk. Calibration ensured that the model predicted the relevant events considered and that it reflected the risk of a much higher-risk population than the one used to derive the equations originally. The rate ratios were determined by the division of the number of CVD events in an analysis of real-world observational data[14,15] and the events predicted by the risk engines,[12,13] controlling for individual patient characteristics (such as age, systolic blood pressure, and diabetes status) for the higher-risk population indicated for PCSK9 inhibitor treatment. We used an analysis of real-world long-term UK data for the ASCVD population, because US claims data are usually limited to <10 years owing to patients switching for changes in employment. The HeFH population in the United States is not well characterized or studied, so we used a study from Europe,[16] where the literature on this topic is available and reliable. Average calibration factors for the ASCVD populations ranged from 2.35 to 5.10 (acute) and 0.92 to 2.56 (long term). Patients with HeFH have a higher baseline CVD risk than the ASCVD population due to longer exposures of higher levels of LDL-C. Therefore, a different rate ratio (7.1; 95% confidence interval [CI]: 5.7-8.7), based on the results of a Danish familial hypercholesterolemia study,[16] was used.[12,13] The resulting calibration factors led to an estimated 10-year risk of ≥1 CVD events of 51% for HeFH and 44% for ASCVD (51% with statin intolerance).

Treatment Efficacy: The predicted effectiveness of evolocumab on reducing CVD event rates was derived from the relative LDL-C reduction from baseline to week 12 observed among evolocumab-treated patients in the clinical program: HeFH,[17] 61% (95% CI: 55%-67%); ASCVD,[17] 71% (61%-81%); and ASCVD with statin intolerance,[8] 56% (52%-60%). The CTTC meta-analysis, analyzing the cardiovascular rate reduction of statin use, was considered.[3] The CTTC rate ratios for CVD events were applied to the rates of events predicted (Table 2).

Mortality: The 2010 US life tables[18] were used to predict all-cause mortality by age and sex. CVD mortality was predicted separately from non-CVD mortality. Non-CVD mortality was further assumed to be the same as that of the general population in the US life tables.

Utility: Baseline utility, where 0 indicates death and 1 indicates full health, applied to the no-CVD health state, was estimated as 0.824 for the US population age >45 years.[19] The utilities for other health states (Table 2) were based on the results of a time tradeoff study.[20] The 1-year time tradeoff method was used to evaluate the acute health states, with the 10-year time tradeoff method used for the chronic health states (Table 2).

Costs: The annual US wholesale acquisition price of evolocumab (US$14 139) was used in the cost-effectiveness analysis, and possible discounts were not accounted for in the model. Statin costs were based on published data (average of Red Book prices and the market share of generic simvastatin and atorvastatin),[21] and medication costs did not include monitoring or management. Costs associated with CVD health states were obtained through US claims data[22,23] (Table 2) with a 3-year horizon. The analysis included the acute and short-term costs for the first year and the long-term costs for years 2 and 3. In the absence of information, non-CVD death events were assumed to not incur any costs.[24] Indirect costs were not included in the base case or scenarios in accordance with the payer perspective used in the analyses.

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Table 2. Rate ratio of CVD Events per 38.67 mg/dL of LDL-C Reduction, Costs, and Utility Values for Health States

Item	Rate Ratio (CI)[a]	Utility (SD)[b]	Direct Cost, $US (SE)[c]
ECVD	0.71 (0.58-0.87)		8096 (307)
ACS[d]	0.71 (0.58-0.87)	0.672 (0.340)	49 604 (693)
IS	0.69 (0.50-0.95)	0.327 (0.456)	44 007 (1042)
HF[e]	0.71 (0.58-0.87)	0.602 (0.456)	45 514 (932)
Post-ACS[d]	NA	0.824 (0.174)	8096 (307)
Post-IS	NA	0.524 (0.377)	8396 (604)
Post-HF	NA	0.571 (0.322)	17 562 (732)
CHD death	0.80 (0.74-0.87)		72 892 (550)
IS death	1 (assumption)		72 892 (550)
Revascularization[f]	0.66 (0.60-0.73)		56 556 (448)

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CI, confidence interval; CTTC, Cholesterol Treatment Trialists' Collaboration; CVD, cardiovascular disease; ECVD, established cardiovascular disease; HF, heart failure; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; SD, standard deviation; SE, standard error; UA, unstable angina; USD, United States dollars.
[a]CIs are 99% except for revascularization, which is 95%. Source: CTTC.[3] ECVD and HF health states were assumed to be equivalent to ACS. IS death was assumed to have a rate ratio of 1, because the rate ratio per 38.67-mg/dL LDL-C reduction was not statistically significant (1.04; 99% CI: 0.77-1.41). [b]In utilities, 0 represents death and 1 represents perfect health. [c]Source: US Claims Data.[22,23] [d]ACS was defined as UA or MI. [e]For transitions from HF to HF and post-HF to HF, the clinical benefit was not applied, reflecting results of statin trials in which LDL-C reduction did not significantly reduce primary composite endpoints in patients with recurrent HF.[38] [f]Revascularization was defined as PCI or CABG.

In evolocumab phase 3 studies, there was a low rate of muscle-related symptoms reported in the statin-intolerant population[8] but no notable differences in the adverse event profiles between evolocumab-treated patients and the placebo-treated patients in the HeFH population[6] or the placebo-treated or ezetimibe-treated patients in the ASCVD population.[7] Based on these findings, the incidence, cost, and impact on health-related quality of life associated with adverse events were not included in the model for any comparator.

Analyses

Base-Case Analysis: Costs, LYs, and QALYs were each discounted at 3%, as recommended by the US Panel on Cost-Effectiveness in Health and Medicine.[25]

As there is no well-defined cost-effectiveness threshold in the US, the predicted incremental cost-effectiveness ratios (ICERs) were compared with cost-effectiveness thresholds[26] from the World Health Organization (WHO) and the statement on level of value[27] from the American College of Cardiology/American Heart Association (ACC/AHA), although some estimates for willingness to pay are much higher (eg, US$300 000/QALY).[28] The WHO thresholds were based on 2014 US gross domestic product per capita (US$54 629.50, World Bank): highly cost-effective, <US$55 000/QALY; cost-effective, US$55 000 to US$165 000/QALY; and not cost-effective, >US$165 000/QALY gained. The ACC/AHA thresholds were based on the level of value to society: high, <US$50 000/QALY gained; intermediate, US$50 000 to < US$150 000/QALY; and low, ≥US$150 000/QALY.

Sensitivity Analyses: To assess the robustness of our results to changes in the input parameters, both univariate deterministic and multivariate probabilistic sensitivity analyses were conducted. When possible, 95% CIs were considered to define the lower and upper bounds and to parameterize the probability distributions. Model inputs included in the sensitivity analyses were LDL-C relative reductions, reductions in rates of CVD events per 38.67-mg/dL LDL-C reduction, health state costs, and utility values.

The relative reduction in LDL-C and the rate reduction in CVD events per 38.67-mg/dL LDL-C reduction were varied by the CIs reported in the clinical trials and the CTTC meta-analysis.[3] The sensitivity analyses of baseline CVD rate calibration factors were set to upper and lower CI bounds from a literature analysis for HeFH patients[29] and registry data for ASCVD patients.[30] For health state costs and utility values, the values were varied based on previously reported CIs for acute and long-term health states.[19,20]

Probabilistic sensitivity analysis was conducted for LDL-C relative reductions, reduction in rates of CVD events, and health state costs and utility values. The base-case analysis used the recommended distributions by Briggs et al[31] (β, LDL-C relative reductions; lognormal, rate reduction per 38.67-mg/dL LDL-C reduction; γ, health state costs; β, health state utility values). Model parameters were randomly sampled 1000 times. The probability of the new intervention being cost-effective for different willingness to pay thresholds was then presented in the cost-effectiveness acceptability curve.

Scenario Analyses: Scenario analyses included reduction in rates of CVD events observed in the evolocumab Open-Label Study of Long-term Evaluation Against LDL Cholesterol (OSLER) studies,[9] no LDL-C–lowering effect on rates of HF, compliance from the OSLER studies,[9] and alternate discount rates. A separate scenario analysis assessed price thresholds at which evolocumab met the ACC/AHA intermediate level-of-value and WHO cost-effectiveness thresholds.

Results

Evolocumab use was associated with a relative reduction in nonfatal CVD event rates ranging from 36% to 61% and a 25% to 43% reduction in CHD death rates according to the model (Table 3). The initial HeFH rate ratio of 7.1 translated into HeFH patients being predicted to have 3.7× more events over a lifetime horizon than non-HeFH patients with a similar risk profile. The incremental costs of evolocumab added to SOC over SOC alone in the HeFH, ASCVD, and ASCVD with statin intolerance populations were US$153 289, US$158 307, and US$136 903, respectively. These populations gained

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Table 3. CVD Event Rates With EvoMab Added to SOC vs SOC Alone, According to the Model

	HeFH				ASCVD				ASCVD (Statin-Intolerant)			
Health State	EvoMab + SOC	SOC	Incre	% Change	EvoMab + SOC	SOC	Incre	% Change	EvoMab + SOC	SOC	Incre	% Change
ACS	0.51	1.02	−0.51	−50	0.36	0.84	−0.48	−57	0.40	1.00	−0.60	−60
IS	0.11	0.23	−0.12	−51	0.06	0.14	−0.08	−58	0.07	0.18	−0.11	−61
HF	0.14	0.22	−0.08	−36	0.14	0.26	−0.11	−44	0.11	0.25	−0.14	−55
CHD death	0.51	0.68	−0.17	−25	0.25	0.41	−0.16	−39	0.25	0.43	−0.18	−43
IS death[a]	0.19	0.14	0.05	33	0.11	0.10	0.01	10	0.13	0.12	0.01	11
Revascularization	0.49	1.14	−0.65	−57	0.40	1.03	−0.62	−61	0.38	1.02	−0.64	−63

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; EvoMab, evolocumab; HeFH, heterozygous familial hypercholesterolemia; HF, heart failure; Incre, incremental; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; SOC, standard of care.
[a]IS death was assumed to have an rate ratio of 1, because the rate ratio per 38.67-mg/dL LDL-C reduction was not statistically significant (1.04; 99% CI: 0.77-1.41). The observed increases in CVD event rates occurred because of longer predicted survival with EvoMab + SOC.

Table 4. Predicted Total Costs, LYs, and QALYs for EvoMab Added to SOC vs SOC Alone

	ICER, US$	Total Cost, US$			Total LY			Total QALY		
Population		EvoMab + SOC	SOC Alone	Incre	EvoMab + SOC	SOC Alone	Incre	EvoMab + SOC	SOC Alone	Incre
HeFH	75 863	341 191	187 902	153 289	14.65	12.37	2.28	11.64	9.62	2.02
Medication		208 122	841	207 282						
Fatal events		28 565	37 052	−8487						
Nonfatal events		22 300	46 137	−23 837	0.46	0.96	−0.49	0.28	0.57	−0.29
Revascularization		18 565	44 638	−26 073						
Long-term health states		63 638	59 234	4404	14.19	11.41	2.78	11.36	9.05	2.31
ASCVD	141 699	381 499	223 192	158 307	13.93	12.64	1.29	10.51	9.39	1.12
Medication		197 973	860	197 113						
Fatal events		16 101	23 515	−7414						
Nonfatal events		17 323	39 019	−21 696	0.36	0.81	−0.45	0.22	0.48	−0.26
Revascularization		16 685	43 082	−26 397						
Long-term health states		133 418	116 716	16 702	13.57	11.83	1.74	10.29	8.91	1.38
ASCVD (statin-intolerant)	100 309	348 006	211 104	136 903	13.11	11.63	1.48	10.15	8.79	1.36
Medication		185 325	0	185 325						
Fatal events		17 439	26 255	−8816						
Nonfatal events		18 330	46 552	−28 222	0.38	0.97	−0.58	0.23	0.57	−0.35
Revascularization		15 906	43 699	−27 793						
Long-term health states		111 007	94 597	16 409	12.73	10.66	2.06	9.92	8.21	1.71

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; EvoMab, evolocumab; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; Incre, incremental; LY, life-year; QALY, quality-adjusted life-year; SOC, standard of care.

lifetime incremental LYs of 2.28, 1.29, and 1.48, as well as QALYs of 2.02, 1.12, and 1.36 (Table 4).

The ICERs of evolocumab added to SOC vs SOC alone were US$75 863/QALY gained in HeFH; US$141 699 in ASCVD; and US$100 309 in ASCVD with statin intolerance. All ICERs met the ACC/AHA intermediate value and WHO cost-effectiveness thresholds.

Univariate Sensitivity Analyses

The ICER for evolocumab added to SOC vs SOC alone in HeFH and ASCVD patients met the WHO very cost-effective/cost-effective and ACC/AHA high/intermediate thresholds under most sensitivity analysis assumptions in the ASCVD population without statin intolerance and all

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of the assumptions in the HeFH and ASCVD with statin intolerance populations (see Supporting Information, Figure 1, in the online version of this article).

Probabilistic Sensitivity Analysis

The probability of evolocumab added to SOC being cost-effective compared with SOC under the WHO and ACC/AHA willingness to pay thresholds was 100% for HeFH and ASCVD with statin intolerance patients, whereas it was 87% and 63%, respectively, for ASCVD patients (for probabilities of acceptance under a range of willingness to pay thresholds, see Supporting Information, Figure 2, in the online version of this article).

Scenario Analyses

The ICER was 23% and 24% lower in the scenario analysis using reduction in rates of CVD with evolocumab added to SOC vs SOC alone from the open-label extension studies. This result reflects a greater CVD event rate reduction (33%) than the one observed in the CTTC statin meta-analysis. All scenario analysis ICERs met the ACC/AHA high/intermediate value and WHO very cost-effective/cost-effective thresholds, except for the scenarios with no LDL-C–lowering effect on HF rates and alternative discount rate of 5% for costs and outcomes analyses in the ASCVD population (neither ACC/AHA threshold; see Supporting Information, Table 2, in the online version of this article).

Evolocumab added to SOC vs SOC alone met willingness to pay thresholds at the following maximum annual costs: ACC/AHA, US$24 300 in HeFH, US$14 800 in ASCVD, and US$19 300 in ASCVD with statin intolerance; WHO, US$26 400 in HeFH, US$16 000 in ASCVD, and US$20 800 in ASCVD with statin intolerance.

Discussion

The presented economic evaluation found that evolocumab priced at an annual cost of US$14 139 added to SOC vs SOC alone had ICERs of US$75 863 in patients with HeFH and US$141 699 in those with ASCVD (US$100 309 in ASCVD with statin intolerance). These ICERs met the WHO cost-effectiveness and ACA/AHA high/intermediate value thresholds[26,27] in all target populations. Sensitivity analyses confirmed the robustness of the model results. Scenario analyses in the ASCVD population and baseline LDL-C >100 mg/dL found that alternative assumptions generally yielded ICERs meeting the ACC/AHA and WHO thresholds.[26,27]

Although the medication cost was higher for evolocumab than for statins, the greater LDL-C–lowering effects and modeled reduction in CVD events among evolocumab-treated patients determined the resulting cost-effectiveness of the medication. The HeFH populations demonstrated better cost-effectiveness than the ASCVD population, which is consistent with the differences in baseline LDL-C levels and particularly cardiovascular risk. The better cost-effectiveness values with HeFH show the importance of studying cost-effectiveness by specific population type.

Overall, our scenario analyses confirmed that changes in major assumptions would likely lead to ICERs that meet ACC/AHA and WHO thresholds. Notably, the scenario using a post-hoc cardiovascular-event reduction from a randomized open-label extension study[9] of evolocumab found a lower ICER than the base case (which used the CTTC rate ratios[3]).

To the best of our knowledge, we present the first published cost-effectiveness data on evolocumab, though the Comparative Effectiveness Public Advisory Council–Institute for Clinical and Economic Review (CEPAC-ICER) has released a technology assessment[32] of PCSK9 inhibitors. This report concludes that PCSK9 inhibition is not cost-effective with current annual costs in the US societal context, and we concluded that there was strong evidence of cost-effectiveness in the US payer context. Several methodological differences between the CEPAC-ICER report and our model should be noted. The CHD Policy model used by CEPAC-ICER underestimates the impact of single risk-factor interventions (eg, cardiovascular risk), a limitation that was noted in the original model publication.[33] The CHD Policy model was intended to model cardiovascular risk in the entire US population not controlled on statins (age 35-74 years) and not high-risk populations. A recent review article included an analysis to externally validate the results from the CHD Policy model.[33] The results from the external validation found in the Supporting Information in the online version of this article demonstrate that the CHD Policy model underestimated incidence of CHD by approximately 50%.[34] The CEPAC-ICER report also does not account for the elevated risk of CVD events among HeFH and ASCVD patients. Other cost-effectiveness models of familial hypercholesterolemia have incorporated this risk,[35–37] as we do in the present study.

Study Limitations

There are several limitations of our study. Our results should be interpreted within the model assumptions; however, the results of multiple sensitivity analyses did not significantly affect our final conclusions. The LDL-C reductions used in the model were based on short-term studies,[6–8] and there is very limited long-term data on evolocumab specifically, or PCSK9 inhibitors generally. The potential CVD event–lowering effect and harms of evolocumab added to SOC have therefore not been established. If the clinical benefit differs from that modeled in this study or significant adverse events emerge, the cost-effectiveness modeling results would be affected. A longer-term, CVD event–driven study (NCT01764633) of evolocumab is ongoing, so we used reductions per 38.67 mg/dL of LDL-C reduction from the CTTC meta-analysis of statin studies to predict impact of LDL-C reduction on CVD event outcomes.[3] The IMPROVE-IT study[4] suggests that LDL-C reduction using a nonstatin may significantly reduce CVD-event risk with derived rate ratio aligned with the CTTC findings, though there are differing viewpoints about the clinical significance of the observed reductions in IMPROVE-IT. Also, rate ratios from the CTTC meta-analysis were used for acute health states in which a statistically significant rate ratio was reported, except for HF, for which the rate ratio was assumed to be the same as ACS, because the literature on CVD event

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reduction with LDL-C reduction is not yet robust. We assumed, however, no LDL-C–reduction impact on HF rates for patients with recurrent HF.[38–40] No LDL-C–lowering effect on HF rates for any transitions was also tested in a scenario analysis (see Supporting Information, Figure 1, in the online version of this article). Finally, our analysis and all conclusions derived from it are only applicable to the HeFH and ASCVD populations with the risk profile described in Table 1. The analysis is not generalizable to a broader population with less severe disease.

Conclusions

When used in patients with HeFH or ASCVD who are unable to control LDL-C levels with maximally tolerated statins and who remain at high risk, addition of evolocumab to SOC may be cost-effective.

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