Alirocumab for Treatment of High Cholesterol: Effectiveness and Value

New Evidence Update

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	CVD Policy Model Group
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About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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Background

ICER's New Evidence Update for alirocumab (Praluent®, Regeneron/Sanofi) is based on results from the ODYSSEY outcomes trial published in the New England Journal of Medicine on November 7, 2018.[1] We used the results published in the manuscript to update our preliminary cost-effectiveness analyses and associated value-based price benchmarks for this drug. ICER's value-based price benchmarks suggest a price range that would align fairly with the added benefits of new treatment options for patients and the health care system.

ICER previously assessed the cost-effectiveness of alirocumab and evolocumab (Repatha®, Amgen Inc.) shortly after these drugs were first granted regulatory approval in the United States in 2015,[2] and performed a New Evidence Update for evolocumab in September 2017 following the release of outcomes data from the FOURIER trial.[3] A preliminary new evidence update for alirocumab was published on March 10, 2018, following presentation of the results at the American College of Cardiology's 2018 Scientific Session.[4,5]

Summary of Clinical Trial Results

The ODYSSEY Outcomes trial[1] was a multi-site randomized controlled trial testing alirocumab versus placebo in patients with the following eligibility criteria: 1) age ≥ 40 years; 2) hospitalization for acute coronary syndrome with myocardial infarction (MI) or unstable angina 1-12 months prior to randomization; 3) a run-in period of 2-16 weeks of high-intensity or maximally-tolerated dose of atorvastatin or rosuvastatin; and 4) following the run-in period, at least one of the following lipid entry criteria: low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL (1.8 mmol/L), non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL (2.6 mmol/L), or Apolipoprotein B ≥80 mg/dL.

In the ODYSSEY Outcomes Trial, the primary outcome was a composite of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), ischemic stroke (fatal and non-fatal), and hospitalization for unstable angina. The incidence of the primary outcome (see Table 1 below) was lower in the alirocumab arm of the trial (hazard ratio [HR]: 0.85, 95% confidence interval [CI] 0.78-0.93). There was a non-significant reduction in CHD death (HR: 0.92) and cardiovascular disease death (HR: 0.88) and a nominally significant reduction in all-cause mortality (HR: 0.85, 95% CI 0.73-0.98).

Table 1. Primary and Key Secondary Outcomes of the ODYSSEY Outcomes Trial

Outcome	Entire Cohort HR (95% CI)
Primary outcome: CHD death, non-fatal MI, ischemic stroke, unstable angina	0.85 (0.78-0.93)
CHD death	0.92 (0.76-1.11)
ASCVD death	0.88 (0.74-1.05)
All-cause death	0.85 (0.73-0.98)

CHD: coronary heart disease, CVD: atherosclerotic cardiovascular disease, HR: hazard ratio, LDL-C: low density lipoprotein cholesterol, MI: myocardial infarction

The prespecified subgroup analysis by baseline LDL-C (<80 mg/dL, 80-100 mg/dL, ≥100 mg/dL) was not significant for the primary endpoint (Table 2). In addition, there was not a dose-response effect by baseline LDL-C level: the hazard ratios for the 80-100 mg/dL group did not fall between the other two groups. In a post-hoc analysis, the absolute benefit of alirocumab was significantly greater in the subgroup of patients with a high baseline LDL-C level (≥100 mg/dL) on maximally tolerated statin therapy ($p < 0.001$ for the primary endpoint, Table 2 below), but this may be a chance finding.

There were dose adjustments of alirocumab based on achieved LDL-C. Among the 9,462 patients assigned to treatment with alirocumab 75 mg every two weeks, 2,615 (27.6%) had up-titration to 150 mg every two weeks; of these, 805 were subsequently down titrated back to 75 mg every two weeks. Patients receiving 75 mg alirocumab who had two consecutive LDL-C measurements below 15 mg/dL were switched to placebo; this occurred with 730 (7.7%) of patients on alirocumab. This protocol raises the possibility that patients with a higher baseline LDL-C might have experienced a greater dose intensity of alirocumab, which could have led to different relative efficacy in the higher LDL-C subgroup. However, no data have been presented to substantiate this hypothesis. Although the data were not new in the recent publication of ODYSSEY,[1] the graphic representation in figure S6 showing LDL-C results over time contrasted with the primary end point hazard ratios, both by baseline LDL-C, led us to conclude in this updated report that differential changes in dose intensity of alirocumab were an unlikely explanation for the results. Patients with a baseline LDL-C between 80 and 100 mg/dL had the smallest reduction in the primary endpoint, while the reductions in LDL-C in this intermediate subgroup were intermediate and similar in shape over time to the other two subgroups, without any discontinuities as might be seen at the time of dose alterations. Additionally, while there is some evidence that differential relative effects on outcomes may be seen in patients with baseline LDL-C above 100 mg/dL,[6] many trials of lipid-lowering therapies that have examined clinical outcomes have shown consistent relative effects across LDL-C levels.[7-9] For example, no differential relative effect across LDL subgroups was seen in the FOURIER trial of evolocumab.[10] Thus, we feel it is appropriate to assume a constant relative effect of alirocumab

across LDL-C levels for our base-case analysis, which is consistent with the non-significant interaction by LDL-C level in the prespecified analysis of the ODYSSEY Outcomes trial.[1]

Table 2. Primary and Secondary Outcomes by Categories of Baseline LDL Cholesterol in the ODYSSEY Outcomes Trial

Outcome	LDL-C Category	HR (95% CI)	P-value for interaction
Primary outcome: CHD death, non-fatal MI, ischemic stroke, unstable angina	<80 mg/dL	0.86 (0.74-1.01)	0.09
	80 to <100 mg/dL	0.96 (0.82-1.14)	
	≥100 mg/dL	0.76 (0.65-0.87)	
CHD death	<80 mg/dL	1.00 (0.73-1.39)	*
	80 to <100 mg/dL	1.17 (0.81-1.68)	
	≥100 mg/dL	0.72 (0.53-0.98)	
ASCVD death	<80 mg/dL	0.96 (0.71-1.29)	*
	80 to <100 mg/dL	1.12 (0.80-1.56)	
	≥100 mg/dL	0.69 (0.52-0.92)	
All-cause death	<80 mg/dL	0.89 (0.69-1.14)	*
	80 to <100 mg/dL	1.03 (0.78-1.36)	
	≥100 mg/dL	0.71 (0.56-0.90)	

*Not reported because the interaction with CHD death was NS.
CI: confidence interval, ASCVD: atherosclerotic cardiovascular disease, HR: hazard ratio, LDL-C: low density lipoprotein cholesterol, MI: myocardial infarction, NS: not significant.

There were no new adverse events identified in the ODYSSEY Outcomes trial. The total number of adverse events and serious adverse events were numerically lower in the alirocumab group. As expected, there were more local injection site reactions in the alirocumab group compared with placebo (3.8% versus 2.1%). There was no increase in new diabetes, neurocognitive events, creatinine kinase elevations, or liver enzyme elevations.

Summary of Updated Cost-Effectiveness Analysis Results

We updated our estimates of the long-term cost-effectiveness of alirocumab based on data from the ODYSSEY Outcomes trial as described above. This analysis was conducted in partnership with an independent research group led by Dr. Dhruv Kazi at Beth Israel Deaconess Medical Center, Boston and Dr. Kirsten Bibbins-Domingo at the University of California, San Francisco. The team used the Cardiovascular Disease (CVD) Policy Model, an established simulation model that systematically combines data from vital statistics, epidemiologic studies, clinical trials, and registries to project the morbidity, mortality, and direct medical costs related to cardiovascular disease in the US population . The model used for this analysis was structurally similar to that previously described in ICER's final report on PCSK9 inhibitors developed as part of deliberations held by the New England Comparative Effectiveness Public Advisory Council in October 2015, which was subsequently published in the peer-reviewed literature.[11-13] As before, the analyses adopted a health system perspective and assessed costs and outcomes over a lifetime horizon. We assumed the annual price of alirocumab to be the US list price announced in February 2019 ($5,850 per year).[14] We applied the reduction in major coronary heart disease (CHD) events and stroke as observed in the ODYSSEY Outcomes trial to CHD and stroke events in the CVD Policy Model to project changes in health outcomes and costs if all patients eligible for alirocumab based on the eligibility criteria of the ODYSSEY Outcomes trial would receive the drug. Cost-effectiveness was presented in terms of incremental cost per quality-adjusted life year (QALY) gained for treatment with alirocumab + statin compared with statin alone among patients who meet the inclusion criteria of the ODYSSEY Outcomes Trial.

We performed additional deterministic and probabilistic sensitivity analyses to examine the robustness of the results to uncertainty in model inputs. In particular, we varied the price of alirocumab to identify the price at which it would become cost-effective relative to statin therapy at willingness-to-pay thresholds of $100,000 per QALY and $150,000 per QALY. In the probabilistic sensitivity analysis, we performed 1,000 trials that varied all key input parameters simultaneously, sampling with replacement from pre-specified statistical distributions. These results were used to create 95% uncertainty intervals (UIs) around the point-estimates of the incremental cost-effectiveness ratio. We also performed a subgroup analysis to examine the cost-effectiveness of alirocumab therapy among patients with a recent MI and a baseline LDL-C ≥100mg/dL despite maximal statin therapy. This high-risk group was assumed to have a higher baseline risk of events compared with the entire trial-eligible population but an identical relative risk reduction as the trial-eligible population (see discussion under Summary of Clinical Trial Results above). See Table 3 below for a description of key differences between the preliminary and final New Evidence Updates and a related analysis published in *Annals of Internal Medicine*.

Table 3. Key Differences Between ICER Preliminary New Evidence Update, Annals Publication, and ICER Final New Evidence Update

Data Element	ICER Preliminary New Evidence Update[4]	Annals Paper[15]	ICER Final New Evidence Update
Base Case			
Intervention	Statin + Alirocumab	Statin + Alirocumab	Statin + Alirocumab
Comparator	Statin alone	Statin + Ezetimibe	Statin alone
Annual cost of Alirocumab	$7186.52	$7186.52	$5850.00[14]
Sensitivity Analyses (LDL-C ≥ 100mg/dL subgroup)			
Baseline MACE Rate (per 100 patient-years)	6.2	7.2*	7.2*
HR for MI and CVD-mortality	Subgroup	Overall	Overall

*The simulation model was further refined between reports to fully capture the increased risk of MACE in this subgroup.
HR: hazard ratio, MACE: major adverse cardiovascular event (a composite of CVD death, non-fatal MI, and non-fatal stroke), MI: myocardial infarction, CVD: cardiovascular disease

Finally, in a scenario analysis, we examined how the results in the subgroup of patients with an initial LDL-C ≥100mg/dL would change if we assumed a higher relative risk reduction, as described in the initial ODYSSEY Outcomes presentation.

Based in part on the biologic plausibility arguments discussed above, some believe there is a greater relative reduction in events in patients with a baseline LDL ≥100 mg/dL. A statistically non-significant interaction term (p = 0.09) does not exclude this possibility and so we performed a scenario analysis in patients with a baseline LDL ≥100 mg/dL using the point estimate for the hazard ratio in that subgroup.

Summary results are presented in Table 4 below. Please see the accompanying peer-reviewed publication for complete methodological details and additional results.[15]

Table 4. ICERs and Threshold Prices, Based on Patient Population

	Incremental Cost Effectiveness Ratio ($/QALY)	Annual Price to Achieve $50,000 /QALY	Annual Price to Achieve $100,000 /QALY	Annual Price to Achieve $150,000 /QALY	Value-Based Price Benchmark Range
Assumes observed reduction in major CHD events					
All eligible patients	$251,000 ($161,000 to $552,000)	$1,138	$2,311	$3,484	$2,311 to $3,484
Only patients with LDL-C ≥100 mg/dL (assuming higher baseline risk but identical relative risk reduction as the entire trial-eligible population)	$218,000 ($139,000 to $484,000)	$1,315	$2,656	$3,997	$2,656 to $3,997

CHD: coronary heart disease, LDL-C: low density lipoprotein cholesterol, MI: myocardial infarction, QALY: quality-adjusted life year

In the scenario analysis in which we assume a higher relative risk reduction in patients with a recent MI and an initial LDL-C ≥100mg/dL than in the entire trial-eligible population, the ICER for alirocumab is $119,000 per QALY (95% UI, $90,000 to $187,000) relative to statin therapy. To achieve a cost-effectiveness threshold of $100,000 per QALY relative to statin therapy, the price of alirocumab would have to decline to $4,928 in this scenario, and to achieve a threshold of $150,000 per QALY, the annual price could be increased to $7,417. We discuss above the basis for our decision to move this analysis from the base case in the preliminary new evidence update to a scenario analysis in this final version. The threshold prices shown here for this scenario are somewhat higher than in the preliminary version because we were able to incorporate more accurate information on the increased risk of events in patients with a higher baseline LDL-C.

Potential Budget Impact

We performed a potential budget impact analysis as part of the final New Evidence Update. Potential budget impact was defined as the total net cost of using alirocumab added to statin treatment compared with statin treatment alone for the treated population, calculated as health care costs (including drug costs) minus any offsets in these costs from averted health care events. Estimates of the eligible population that are likely to be considered for PCSK9 inhibitor treatment have been contentious. For this update, we used an estimate of the eligible population of US adults aged 40-80 years with ASCVD and LDL-C ≥70 mg/dL despite statin therapy. Kazi et al. have estimated this population as approximately 8,947,000 individuals in the US in 2015, based on 2005-2012 National Health and Nutrition Examination Surveys (NHANES).[12] All costs were undiscounted

and estimated over a five-year time horizon, assuming equal uptake over each of the five years (i.e., 20% of 8,947,000, or 1,789,400 patients per year).

ICER's methods for estimating potential budget impact are described in detail elsewhere and have been recently updated.[16] The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

Table 5 illustrates the per-patient budget impact calculations for alirocumab treatment, based on the most recent list price of $5,850 per year and the prices to reach $150,000, $100,000, and $50,000 per QALY ($3,484, $2,311, and $1,138 per year, respectively), compared to statin only.

Table 5. Per-Patient Budget Impact Calculations for Alirocumab plus Statin Compared to Statin Only, Over a Five-Year Time Horizon

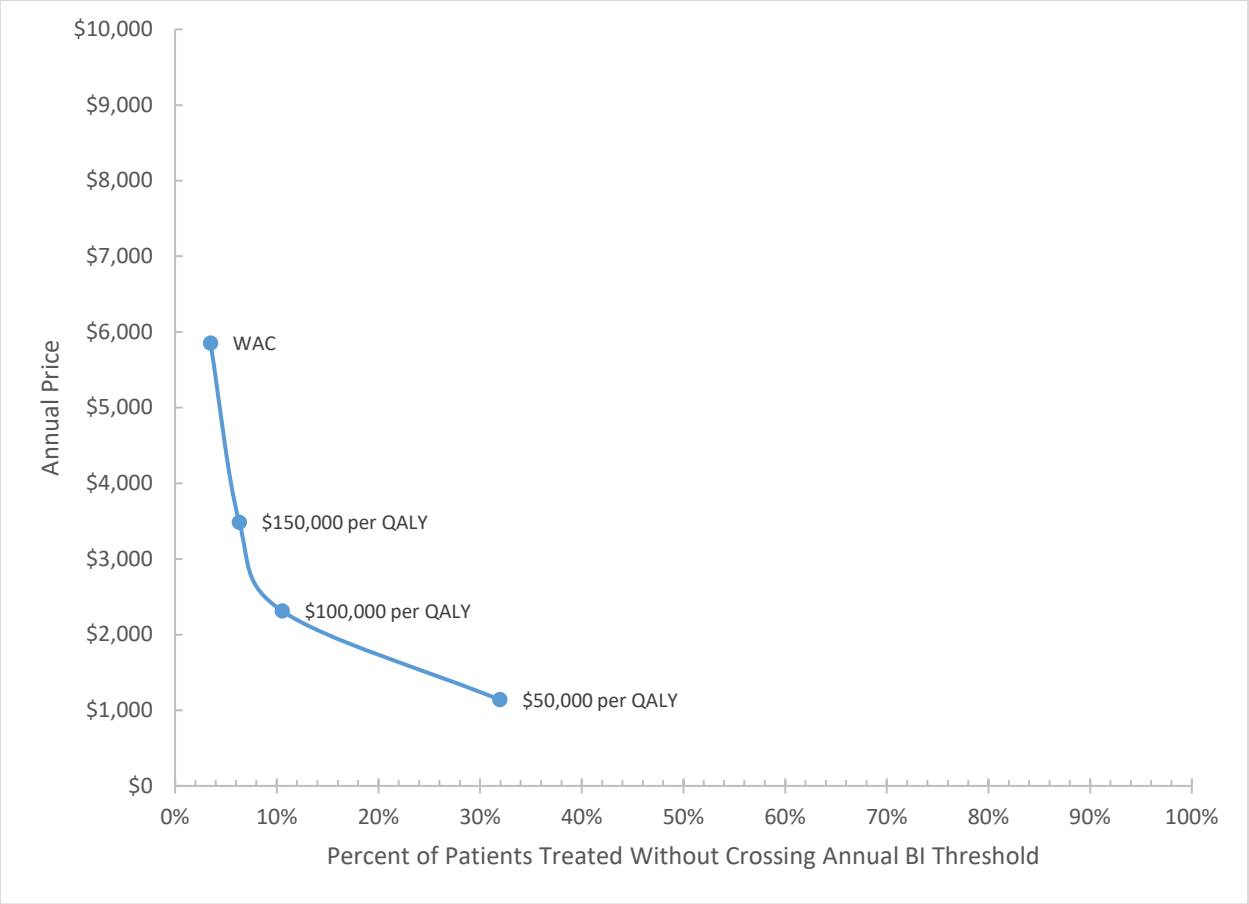
	Average Annual per Patient Budget Impact			
	List Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Alirocumab + Statin	$32,138	$29,772	$28,599	$27,426
Statin	$26,847			
Difference	$5,291	$2,925	$1,752	$579

QALY: quality-adjusted life year

The average potential budgetary impact compared to statin only when using the current list price was an additional per-patient cost of approximately $5,300. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately $2,900 per patient using the annual price to achieve $150,000 per QALY ($3,484) to approximately $580 per patient using the annual price to achieve a $100,000 per QALY cost-effectiveness threshold ($1,138).

As shown in Figure 1, approximately 3% of eligible patients could be treated in a given year without crossing the ICER annual budget impact threshold of $991 million at alirocumab's current list price. Approximately 6% of the eligible population could be treated before exceeding the $991 million threshold at the $150,000 per QALY threshold price and approximately 11% at the $100,000 per QALY threshold price, increasing up to approximately 32% at the $50,000 per QALY threshold price.

Figure 1. Potential Budget Impact Scenarios at Different Prices of Alirocumab Treatment



As illustrated in the above analysis, treating the entire potentially eligible population with alirocumab therapy would result in a substantial budget impact. While it is unclear if these therapies will likely be prescribed more narrowly or in the larger population indicated by the drug's FDA label, policymakers may need to continue to evaluate strategies to ensure affordable access to alirocumab.

Comment

The new evidence from the ODYSSEY Outcomes trial does not alter ICER's cost-effectiveness assessment for another PCSK9 inhibitor, evolocumab. In September 2017, after assessing new data from the FOURIER outcomes trial, ICER announced that the value-based price benchmark for a year's treatment with evolocumab would change to a range from approximately $1,700 to $2,200. The primary reason that this price range is lower than the updated range calculated for alirocumab is that, although the FOURIER trial showed that evolocumab combined with statin therapy is effective in reducing the incidence of cardiovascular events such as MI and stroke, the evidence did

not demonstrate a reduction in CV or all-cause mortality. In contrast, the point estimates for CV and all-cause mortality in ODYSSEY (0.88 and 0.85, respectively) were consistent with the reduction seen in CV events, although under the hierarchical statistical analysis, neither result was statistically significant.

The degree of LDL-C reduction observed in both the ODYSSEY Outcomes and FOURIER trials was similar. Thus, under the LDL hypothesis (the hypothesis that the magnitude of the benefit from lipid therapy is proportional to the magnitude of the LDL reduction regardless of the agent used to lower LDL-cholesterol) one would expect that the outcomes would be similar.[17] However, not all trial results have been consistent with the LDL hypothesis, and it is difficult to ascribe a class effect to PCSK9 inhibitors based on the available evidence. There are several possible explanations for why ODYSSEY Outcomes suggested a mortality benefit for alirocumab while FOURIER found no such signal for evolocumab. First, this may be related to differences in the populations enrolled in the trials: ODYSSEY Outcomes included only patients who had experienced an acute coronary syndrome in the preceding 12 months and these patients may have derived a greater benefit from PCSK9 inhibitor therapy. Second, the apparent difference between the two trials may be a chance finding. Finally, there may be actual differences in the clinical effectiveness of the two drugs. While we feel that it is not possible to be certain of the explanation for the differing results in ODYSSEY Outcomes and FOURIER, clinicians and patients must consider the possibility that these reflect true differences in the effects on mortality of alirocumab and evolocumab.

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