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Cost-Effectiveness of Alirocumab

A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial

Dhruv S. Kazi, MD, MSc, MS; Joanne Penko, MS, MPH; Pamela G. Coxson, PhD; David Guzman, MSPH; Pengxiao C. Wei, BS, MPH; and Kirsten Bibbins-Domingo, PhD, MD, MAS

Background: The ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial included participants with a recent acute coronary syndrome. Compared with participants receiving statins alone, those receiving a statin plus alirocumab had lower rates of a composite outcome including myocardial infarction (MI), stroke, and death.

Objective: To determine the cost-effectiveness of alirocumab in these circumstances.

Design: Decision analysis using the Cardiovascular Disease Policy Model.

Data Sources: Data sources representative of the United States combined with data from the ODYSSEY Outcomes trial.

Target Population: U.S. adults with a recent first MI and a baseline low-density lipoprotein cholesterol level of 1.81 mmol/L (70 mg/dL) or greater.

Time Horizon: Lifetime.

Perspective: U.S. health system.

Intervention: Alirocumab or ezetimibe added to statin therapy.

Outcome Measures: Incremental cost-effectiveness ratio in 2018 U.S. dollars per quality-adjusted life-year (QALY) gained.

Results of Base-Case Analysis: Compared with a statin alone, the addition of ezetimibe cost $81 000 (95% uncertainty interval [UI], $51 000 to $215 000) per QALY. Compared with a statin alone, the addition of alirocumab cost $308 000 (UI, $197 000 to $678 000) per QALY. Compared with the combination of statin and ezetimibe, replacing ezetimibe with alirocumab cost $997 000 (UI, $254 000 to dominated) per QALY.

Results of Sensitivity Analysis: The price of alirocumab would have to decrease from its original cost of $14 560 to $1974 annually to be cost-effective relative to ezetimibe.

Limitation: Effectiveness estimates were based on a single randomized trial with a median follow-up of 2.8 years and should not be extrapolated to patients with stable coronary heart disease.

Conclusion: The price of alirocumab would have to be reduced considerably to be cost-effective. Because substantial reductions already have occurred, we believe that timely, independent cost-effectiveness analyses can inform clinical and policy discussions of new drugs as they enter the market.

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Alirocumab is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin 9 (PCSK9). It was approved in 2016 by the U.S. Food and Drug Administration for patients with heterozygous familial hypercholesterolemia or preexisting atherosclerotic cardiovascular disease who require additional lipid-lowering despite maximally tolerated doses of statin therapy. This approval was based on trials showing a 50% to 60% reduction in low-density lipoprotein cholesterol (LDL-C) levels (1). Since its approval, alirocumab has been available at a wholesale acquisition cost of more than $14 000, a price that is not cost-effective on the basis of the cardiovascular benefit that may be expected from the amount of LDL-C lowering (2).

In March 2018, the results of the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial were announced at the American College of Cardiology Annual Scientific Sessions (3). This was the first trial powered to evaluate the effect of alirocumab on cardiovascular events. The study participants had a history of acute coronary syndrome in the previous 4 to 52 weeks and an LDL-C level of 1.81 mmol/L (70 mg/dL) or greater despite statin therapy. The results established that when alirocumab was added to high-intensity statin therapy, at a median follow-up of 2.8 years participants had a 15% reduction in a composite outcome of nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for unstable angina, and coronary heart disease death, as well as a 15% reduction in all-cause mortality (3, 4). Here, we report how we used these results to examine the cost-effectiveness of alirocumab in the population of U.S. patients with a recent history of acute coronary syndrome by projecting the lifetime incremental health gains, costs, and cost-effectiveness of adding alirocumab to high-intensity statin therapy. We performed this analysis initially to coincide with the public presentation of the trial results in March 2018, and we now confirm the analysis on the basis of the peer-reviewed article published by the ODYSSEY trialists in November 2018 (3, 4).

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Table 1. Selected Input Parameters for the Cardiovascular Disease Policy Model

Input Parameter	Base-Case Value	Range for Sensitivity Analysis	Distribution for Monte Carlo Simulations	Reference
Intervention effect sizes				
Ezetimibe*				
Relative rate of MI and coronary heart disease death†	0.91	0.85–0.98	Log-normal	13
Relative rate of ischemic stroke	0.79	0.67–0.94	Log-normal	13
Alirocumab‡				
Relative rate of MI and coronary heart disease death§	0.88	0.80–0.96	Log-normal	3, 4
Relative rate of ischemic stroke	0.73	0.57–0.93	Log normal	3, 4
Costs, *2018 US $*				
Annual drug costs				
Ezetimibe	1410.94	304.38–5250.48	–	24, 25
PCSK9 inhibitor	7186.52	3640.00–18 200.00	–	24, 25
Coronary heart disease				
Acute fatal MI hospitalization	56 275	46 897–67 530	Log-normal	10–12
Acute nonfatal MI hospitalization	40 728	33 939–48 873	Log-normal	10–12
Acute nonfatal MI and CABG hospitalization	104 106	86 775–124 927	Log-normal	10–12
Acute MI care for the first year after hospitalization	12 962	10 802–15 555	Log-normal	10–12
Coronary heart disease care in subsequent years	2648	2206–3177	Log-normal	9, 10
Heart failure hospitalization	20 499	17 083–24 598	Log-normal	10–12
Stroke care				
Fatal stroke hospitalization	28 050	23 374–33 660	Log-normal	10–12
Nonfatal stroke hospitalization	20 730	17 275–24 876	Log-normal	10–12
Care 2–11 mo after stroke	36 468	30 391–43 762	Log-normal	10–12
Poststroke care in subsequent years	5573	4645–6688	Log-normal	9, 10
Quality of life				
Chronic conditions‖				
No history of cardiovascular disease	1.0000	–	–	Assumed
History of angina	0.9000	0.8667–0.9393	β	17–19
History of revascularization for angina¶	0.9864	0.9819–0.9917	β	14, 17–19
History of MI	0.9648	0.9505–0.9758	β	17–19
History of stroke	0.8835	0.8414–0.9108	β	17–19
History of MI and stroke	0.8524	0.7997–0.8888	β	17–19
Deductions for acute events, *d*				
Angina	0.40	11.1–24.36	β	17–19
Revascularization**	5.11	2.56–7.67	β	14
Acute MI	2.89	1.86–4.09	β	17–19
Acute MI and revascularization††	8.00	4.42–11.76	β	Estimated
Acute stroke	4.13	3.07–5.62	β	17–19
Injection site adverse reactions	0.11	0–0.73	β	15, 16

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCSK9 = proprotein convertase subtilisin/kexin type 9.
* The effect of ezetimibe was modeled by calibrating the rate ratio for coronary heart disease and stroke to the results of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (13). The model assumed a constant risk reduction in MI and stroke throughout the simulated time horizon.
† To model the effect of ezetimibe on coronary events, we used outcome data from IMPROVE-IT for a secondary end point defined as "death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days."
‡ The effect of alirocumab was modeled by calibrating the rate ratio for coronary heart disease and stroke to the results of the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial (3). The model assumed a constant risk reduction in MI and stroke throughout the simulated time horizon.
§ To model the effect of alirocumab on coronary events, we used outcome data from ODYSSEY Outcomes for major coronary heart disease events, defined as nonfatal MI and death from coronary heart disease. We assumed that any reduction in all-cause mortality was mediated through a reduction in risk for events related to coronary heart disease or stroke. As a result, we applied the reported reduction in major coronary heart disease events to both fatal and nonfatal coronary heart disease events and, similarly, the reduction in ischemic stroke events to fatal and nonfatal ischemic strokes. We did not model any direct effect on all-cause mortality other than through the effect of the drug on coronary heart disease and stroke outcomes.
‖ Based on a scale of 0 to 1.
¶ Estimated by linear interpolation between the quality of life with angina and perfect health.
** Indicates the weighted average of disutility related to percutaneous and surgical revascularization.
†† Indicates the sum of the reduction associated with an MI and a revascularization procedure.

METHODS

Model Overview

The Cardiovascular Disease Policy Model is an established state-and-transition computer simulation program that projects the incidence, prevalence, and costs associated with coronary heart disease and stroke among U.S. adults aged 35 to 94 years (Supplement Figure 1, available at Annals.org) (2, 5–7). The model is programmed in Lahey Fortran 95; Monte Carlo simulations are programmed in Python (Python Software Foundation).

For persons who have incident angina, MI, stroke, or cardiac arrest, the model projects clinical outcomes that include hospitalizations, revascularization proce-

dures, and death; quality-adjusted survival; and direct medical costs associated with the event. In the population that survives the initial cardiovascular event, the model predicts recurrent cardiovascular events, quality-adjusted survival, and direct medical costs associated with inpatient and outpatient care up to age 95 years or death from any cause, whichever occurs first. The model adopts a health system perspective, capturing all direct health care costs and health benefits, regardless of who accrues them, and a lifetime analytic horizon, following all persons until they die or reach the age of 95 years, whichever is sooner. Costs and utilities are assigned to each clinical event and health state in annual cycles, and future costs and outcomes are discounted at 3% per year (Supplement Figure 1 and Supplement Tables 1 to 4, available at Annals.org) (8).

We derived model inputs from epidemiologic studies, claims data, randomized trials, vital statistics, and the U.S. Census (Table 1) (3, 9–27), and calibrated the model to reproduce U.S. national data on MI, stroke, and death from cardiovascular causes or any cause in 2010 as observed in the National Hospital Discharge Survey and national vital statistics (Supplement Table 4) (22, 23). The institutional review board at the University of California, San Francisco, approved research with the model. This analysis was performed independent of the ODYSSEY Outcomes sponsor and academic steering committee.

Target Population

For this analysis, we adapted the model to approximate the inclusion criteria for the ODYSSEY Outcomes trial. We modeled a cohort of U.S. adults aged 40 years and older who had an MI 1 to 12 months before enrollment and had an LDL-C level of 1.81 mmol/L (70 mg/dL) or greater despite statin therapy. We based the initial characteristics of this cohort on the 2005 to 2012 NHANES (National Health and Nutrition Examination Survey) (20). With regard to participants who met other inclusion criteria but were not receiving statins, we first modeled them as initiating statin therapy so that their mean LDL-C level equaled that of patients receiving statin therapy; then, we included persons in the simulation if their LDL-C level remained at 1.81 mmol/L (70 mg/dL) or higher despite statin therapy.

Treatment Strategies

We conducted our baseline analysis with patients who were receiving only a statin, as identified in the 2005 to 2012 NHANES (20). We modeled 2 additional treatment strategies: the addition of ezetimibe to statin therapy (ezetimibe is the recommended second-line agent for lipid lowering) and the addition of alirocumab to statin therapy. These approaches enabled us to compare a statin alone with either a statin plus ezetimibe or a statin plus alirocumab and to compare a statin plus alirocumab with a statin plus ezetimibe.

Table 1 describes how we modeled the effect of adding ezetimibe or alirocumab to statin therapy. We assumed that any reduction in all-cause mortality was mediated through a reduction in the risk for death related to coronary heart disease or stroke. We also estimated that 3.8% of patients receiving alirocumab would have injection site reactions, which would produce a small quality-of-life penalty without an increase in costs or treatment discontinuation (3, 4).

Cost and Quality-of-Life Estimates

We estimated direct health care costs from U.S. national data (Table 1) and adjusted them to 2018 U.S. dollars by using the medical component of the Consumer Price Index (9–12, 28). In the base case, we assumed that annual drug costs were equal to the U.S. prices in 2018 for brand-name ezetimibe and for alirocumab net of rebates and discounts before the change in May 2018, but we varied these prices in sensitivity analyses. We used health-related quality-of-life weights for atherosclerotic cardiovascular disease states based on the Global Burden of Disease 2010 Study (17–19).

Outcomes

Primary outcomes were the projected number of events averted in the population and the incremental cost-effectiveness ratio (ICER) measured in 2018 U.S. dollars per quality-adjusted life-year (QALY) gained over the lifetime analytic horizon. Secondary outcomes were the number of patients who would need to receive treatment for 5 years to avert 1 major adverse cardiovascular event (MACE, defined in this study as a composite of cardiovascular death, nonfatal MI, or nonfatal stroke) and the price of alirocumab at which it would become cost-effective (relative to a statin alone or to a statin plus ezetimibe) at a willingness-to-pay

Table 2. Baseline Characteristics of the Model Population Compared With Patients Enrolled in the ODYSSEY Outcomes Trial

Characteristic	Model Population (n = 215 000)*	ODYSSEY Outcomes Trial Population (n = 18 924)
Mean age, *y*	67.3	58.6
Female, %	39.5	25.2
LDL-C level		
mmol/L	2.67	2.39
mg/dL	103.2	92.4
HDL-C level		
mmol/L	1.34	1.15
mg/dL	51.6	44.3
Mean body mass index, kg/m^2	30.9	28.5
Hypertension, %	74.7	67.4
Diabetes mellitus, %	30.4	28.8
MACE rate per 100 patient-years in patients receiving a statin alone†	6.2	4.2

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular events; ODYSSEY Outcomes = Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab.
* Sample size indicates the number of U.S. adults in the Cardiovascular Disease Policy Model who were aged ≥40 y at enrollment, had an incident myocardial infarction in the previous 1–12 mo, and had an LDL-C level ≥1.81 mmol/L (≥70 mg/dL) despite statin therapy.
† Indicates annualized MACE rates observed in the calibrated model over the first 3 y compared with annual event rates observed in the control group over the duration of the ODYSSEY Outcomes trial (median follow-up, 2.8 y). MACE was defined as a composite of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes.

Table 3. Lifetime Effectiveness, Direct Health Care Costs, and Incremental Cost-Effectiveness of Adding Alirocumab or Ezetimibe to Statin Therapy Among Patients With Recent MI*

Treatment Strategy	Total CV Events Averted, *n*	NNT for 5 Years to Avert 1 MACE†	Life-Years Gained, *n*	QALYs Gained, *n*
Incremental treatment with ezetimibe compared with a statin alone	12 500 (4567 to 20 100)	41 (25 to 93)	78 200 (30 100 to 124 300)	44 500 (16 300 to 72 000)
Incremental treatment with alirocumab§				
Compared with a statin alone	16 600 (7300 to 26 600)	31 (19 to 76)	104 100 (43 400 to 166 400)	59 100 (26 000 to 93 700)
Compared with statin + ezetimibe	4200 (–7652 to 12 800)	126 (inferior to 998)	25 900 (–48 300 to 166 449)	14 600 (–26 600 to 58 500)

CV = cardiovascular; ICER = incremental cost-effectiveness ratio; MACE = major adverse cardiovascular events; MI = myocardial infarction; NNT = number needed to treat; QALY = quality-adjusted life-year.
* This analysis included patients with a history of an incident MI 1–12 mo before enrollment and a low-density lipoprotein cholesterol level ≥1.81 mmol/L (≥70 mg/dL) when receiving statin therapy (*n* = 215 000). The model assumed the health system perspective and a lifetime analytic horizon, as well as discounted future costs and QALYs at 3% per year. To reflect the precision of the model, person-years of treatment were rounded to the nearest hundred thousand, MACEs and QALYs were rounded to the nearest hundred, costs were rounded to the nearest million, and ICERs were rounded to the nearest thousand. Values are point estimates from the base case (95% uncertainty intervals from probabilistic sensitivity analyses). Additional modeling details are available in the **Supplement** (available at Annals.org).
† MACE was defined as a composite of nonfatal MI, nonfatal stroke, and death from CV causes.
‡ Included age-specific background health care costs (i.e., health care costs unrelated to management of CV disease).
§ Statin plus alirocumab was first compared with a statin alone to replicate the strategies examined in the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial. Next, we compared the statin plus alirocumab group with a statin plus ezetimibe, the next best clinical alternative (and technically the appropriate comparator for an economic analysis of alirocumab in this setting).

threshold of $100 000 per QALY. We also estimated the change in total health care expenditures if all patients meeting the inclusion criteria of the ODYSSEY Outcomes trial received alirocumab. For this analysis, we assumed the perspective of a health plan whose beneficiaries are similar to the general U.S. population, and we estimated incremental health care spending over 5 years per 100 000 beneficiaries aged 40 to 94 years.

Sensitivity Analysis

We performed deterministic and probabilistic sensitivity analyses (across the ranges shown in Table 1) to examine the effect of uncertainty in input parameters on model results. In 1-way sensitivity analyses, we varied 1 input parameter at a time, holding all other parameters at their base values. We substantially varied the drug prices, including lowering the cost of ezetimibe to the median U.S. price for available generic formulations. We also varied the discount rate for future costs and benefits (8). In addition, we identified the price at which alirocumab would be cost-effective at the conventional willingness-to-pay threshold of $100 000 per QALY. We repeated this analysis for the subgroup of patients with a baseline LDL-C level above 2.59 mmol/L (100 mg/dL), assuming a higher baseline risk of events but an identical relative reduction in the risk for MACE (4). In probabilistic sensitivity analyses, we varied several input parameters across prespecified statistical distributions 1000 times to derive 95% uncertainty intervals (UIs).

Statistical Analysis

Outcomes were analyzed by using Python, QB64 (Microsoft), and Excel 2011 (Microsoft); statistical analyses were performed by using SAS, version 9.4 (SAS Institute), and R, version 3.4 (The R Foundation).

Role of the Funding Source

The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Base-Case Analysis

We modeled a population of 215 000 U.S. adults who had an incident MI in the 1 to 12 months before enrollment and had an LDL-C level of 1.81 mmol/L (70 mg/dL) or greater despite statin therapy (Table 2). This population was 39.5% female and had a mean age of 67.3 years and a mean LDL-C level of 2.67 mmol/L (103.2 mg/dL). Approximately 30.9% had diabetes mellitus, and 74.7% had hypertension. The patients in this population had more comorbid conditions than those enrolled in the ODYSSEY Outcomes trial (3, 4). The rate of the composite end point was 6.2 per 100 patients per year in the model population compared with 4.2 per 100 patients per year in the ODYSSEY Outcomes trial (Table 2).

According to our model, compared with a statin alone, adding ezetimibe to statin therapy would avert 12 500 MACE and produce 44 500 additional QALYs over the lifetime horizon at a cost of $3.6 billion for an ICER of $81 000 (95% UI, $51 000 to $215 000) per QALY (Table 3). In addition, compared with a statin alone, adding alirocumab to statin therapy would avert 16 600 MACE and produce 59 100 additional QALYs for an ICER of $308 000 (UI, $197 000 to $678 000) per QALY. Moreover, replacing statin plus ezetimibe with statin plus alirocumab would produce an ICER of $997 000 (UI, $254,000 to dominated) per QALY. The number of patients who would need to receive treatment for 5 years to avert 1 MACE was 31 for a statin

Table 3–Continued

Incremental Drug Cost, *2018 US $ (million)*	Incremental Cost of CV Care, *2018 US $ (million)*	Incremental Cost of Non-CV Care, *2018 US $ (million)*‡	ICER	
			$/Life-Year Saved	*$/QALY*
3530 (3487 to 3572)	–804 (–293 to –1300)	871 (312 to 1407)	78 000 (49 000 to 206 000)	81 000 (51 000 to 215 000)
18 093 (17 835 to 18 362)	–1071 (–471 to –1709)	1160 (511 to 1839)	297 000 (191 000 to 648 000)	308 000 (197 000 to 678 000)
14 564 (14 296 to 14 837)	–266 (–1071 to 493)	289 (–528 to 1162)	962 967 (246 000 to dominated)	997 000 (254 000 to dominated)

plus alirocumab relative to a statin alone and 126 for a statin plus alirocumab relative to a statin plus ezetimibe (Table 3).

Budget Impact Analysis

For every 100 000 beneficiaries aged 40 to 94 years, a health plan should expect to spend an additional $3 186 000 over 5 years if it provides alirocumab to all patients who meet the inclusion criteria of the ODYSSEY Outcomes trial.

Sensitivity Analysis

Although the results are robust to a wide range of assumptions about model inputs, they are sensitive to drug prices (Figures 1 and 2; Supplement Figures 2 to 4, available at Annals.org). In a comparison between a statin plus alirocumab and a statin alone, for the ICER of alirocumab to be equal to $100 000 per QALY, the annual price of alirocumab would have to be reduced by 84%, from its wholesale acquisition cost of $14 536 (during March 2018) to $2311 (Supplement Figure 3). In a comparison between a statin plus alirocumab and a statin plus ezetimibe, for the ICER of alirocumab to be equal to $100 000 per QALY, the annual price of alirocumab would have to be reduced by 86%, to $1974 (Supplement Table 5, available at Annals.org). If we use the median wholesale cost of generic ezetimibe ($304.38) instead of the cost of the brand-name drug, the ICER for replacing a statin plus ezetimibe with a statin plus alirocumab increases to $1 187 000 (UI, $300 000 to dominated) per QALY (Supplement Table 6, available at Annals.org), and the cost of alirocumab would have to decrease to $874 for it to meet the cost-effectiveness threshold of $100 000 per QALY.

Patients with a baseline LDL-C level above 2.59 mmol/L (100 mg/dL) have an elevated baseline MACE rate of 7.2 per 100 patient-years while receiving a statin alone. Among these patients, the ICER for a statin plus alirocumab improves to $269 000 (UI, $171 000 to $595 000) per QALY relative to a statin alone and to $876 000 (UI, $232 000 to dominated) per QALY relative to a statin plus ezetimibe. For these patients, the price of alirocumab would have to decrease to $2656 for the statin–alirocumab combination to be cost-effective relative to a statin alone and to $2055 for it to be cost-effective relative to a statin plus ezetimibe.

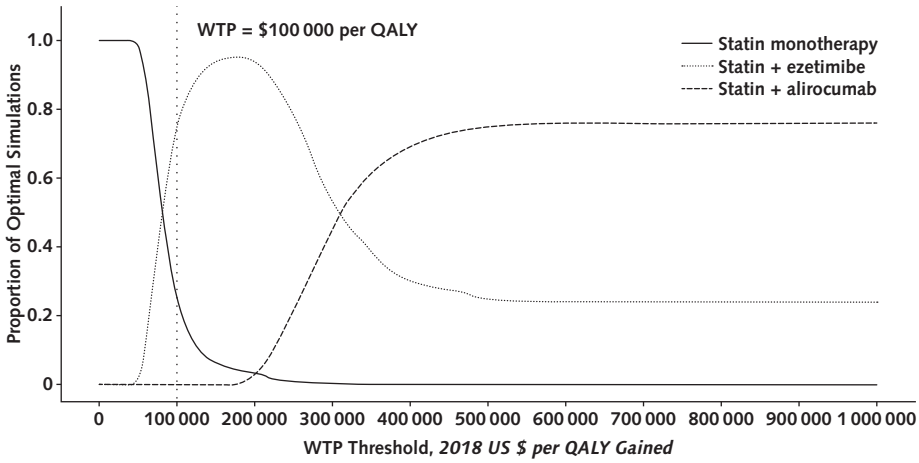
Discussion

For the U.S. population aged 40 years and older with a recent MI and an elevated LDL-C level despite statin therapy, we project that adding alirocumab to statins would avert many MIs, strokes, and cardiovascular deaths. Despite the substantial cardiovascular benefit of alirocumab, its wholesale price, which was $14 560 annually in March 2018 when the results of the ODYSSEY Outcomes trial were first presented, would have to be reduced by 86% to meet a conventional willingness-to-pay threshold of $100 000 per QALY. For alirocumab to be cost-effective relative to generic ezetimibe, its annual price would have to be reduced to $874, which would be unprecedented for biologic therapies in the U.S. market.

One approach to improving the cost-effectiveness of a preventive therapy is to target its use to a subpopulation at the highest risk for preventable outcomes (29, 30). Figure 2 illustrates how, in the case of alirocumab, even this approach would fail to achieve an ICER that would meet the threshold of $100 000 per QALY. To achieve cost-effectiveness at conventional willingness-to-pay thresholds, a substantial reduction in the price of alirocumab must accompany the use of this drug, even in high-risk populations.

Early experience with PCSK9 inhibitors in the United States suggests that their high cost has been a substantial barrier to widespread adoption. A study examining PCSK9 inhibitor prescriptions for 45 029 patients in

Figure 1. Acceptability curves.



Results of probabilistic sensitivity analyses are presented as acceptability curves, which summarize the effect of uncertainty in input parameters on the result of an economic evaluation. The figure shows a range of cost-effectiveness thresholds (on the *x*-axis) against the probability that a given strategy for secondary prevention of cardiovascular disease is cost-effective at that threshold (on the *y*-axis). The 3 lipid-lowering strategies included in this cost-effectiveness analysis were a statin alone (*solid line*), a statin plus ezetimibe (*dotted line*), and a statin plus alirocumab (*dashed line*). At a WTP threshold of $100 000 per QALY gained (*vertical dotted line*), the optimal treatment strategy would be a statin alone in 25.8%, a statin plus ezetimibe in 74.2%, and a statin plus alirocumab in 0% of the simulations. QALY = quality-adjusted life-year; WTP = willingness-to-pay.

the first year after U.S. Food and Drug Administration approval showed that only 47% of prescriptions received payer approval, and this approval was unrelated to the patients' baseline LDL-C level or statin use (31). Among prescriptions that were approved by the payer, 31% were not filled by patients, most often because of high out-of-pocket costs. Our analysis of 2575 Medicare Part D plans across 50 states and the District of Columbia estimated that a Medicare Part D beneficiary receiving only a generic high-intensity statin and a PCSK9 inhibitor would face annual out-of-pocket costs of approximately $5000 (32). Therefore, many patients are not receiving these drugs, either because of lack of payer approval or prohibitive out-of-pocket costs. Novel pricing models, such as refunding drug costs for patients who have an MI or a stroke while receiving a PCSK9 inhibitor, would not meaningfully reduce drug costs for payers because of the relatively low rate of these outcomes in patients who meet indications for PCSK9 inhibitors (33). Lowering the price of these drugs seems to be the most effective way to remove these barriers.

We released a preliminary version of this cost-effectiveness analysis when the ODYSSEY Outcomes trial results were first announced (34). We timed that release to prompt discussion about the pricing of alirocumab (35–37), and we believe it stimulated negotiations by payers to lower the price of the drug. For example, in the weeks that followed, the manufacturer of alirocumab announced large rebates to pharmacy benefit managers to bring the drug's cost within the range deemed to be cost-effective in that analysis, in exchange for payers relaxing some of their restrictions on the drug's use (38). The first such agreement, announced on 1 May 2018, covered 25 million patients whose pharmacy benefits were managed by Express Scripts. We hope that other payers, pharmacy benefit managers, and manufacturers will follow suit. In another encouraging development, the manufacturer of evolocumab, the other PCSK9 inhibitor approved for use in the United States, recently announced a 60% reduction in its list price (39). Reducing the list price will directly lower patients' out-of-pocket costs, whereas the rebates and discounts being offered by the manufacturer of alirocumab lower the cost for payers but often leave patients' out-of-pocket costs unchanged, particularly for Medicare Part D beneficiaries.

Such large reductions in the price of PCSK9 inhibitors are unprecedented among biologic therapies in the United States, where prices for most popular biologics typically increase 10% to 15% each year for a decade after launch. These price reductions are probably driven by lower-than-projected sales of PCSK9 inhibitors, which are the result of cost concerns among patients and payers, and may have been affected by other cost-effectiveness analyses (29).

Cost-effectiveness analyses must be updated periodically as new information about the effectiveness, safety, and price of a therapy and relevant comparators becomes available. In the case of PCSK9 inhibitors, the effect size seen in the ODYSSEY Outcomes trial is somewhat smaller than that predicted by the magnitude of LDL-C lowering seen in earlier trials (2, 40). At the same time, the cost of ezetimibe decreased substantially since our initial analysis because of large discounts on branded ezetimibe and the availability of generic formulations. Both these factors have increased our estimates of the ICER for alirocumab therapy relative to ezetimibe over time. This increase has been offset only partially by the inclusion of patients at higher baseline risk in this study (2). The National Academy of Medicine previously recommended continuous evaluation of a drug's benefit–risk profile during the entire

market life of the product; we contend that this approach is just as critical for cost-effectiveness evaluations (41, 42).

This study had several limitations. The cohort was limited to patients presenting with their first MI and did not model patients presenting with unstable angina (17% of ODYSSEY Outcomes trial participants). To the extent that quality-adjusted survival and MACE rates during follow-up in these subpopulations were similar to those of the post-MI patients we modeled, this exclusion would not materially affect our cost-effectiveness estimates (43). This study did not evaluate the cost-effectiveness of alirocumab in statin-intolerant patients, because a run-in period of statin use in the ODYSSEY Outcomes trial ensured that more than 97% of participants were receiving statin therapy. We previously showed that higher baseline event rates among patients not receiving statins resulted in a modest improvement in the cost-effectiveness of PCSK9 inhibitors in this subgroup (2). Our model extrapolated that the efficacy of alirocumab as observed over a median follow-up of 2.8 years in the ODYSSEY Outcomes trial would be sustained over the long term, which must be ascertained in studies with longer follow-up. The effectiveness of ezetimibe and alirocumab was estimated from 1 large randomized trial of each drug, thus limiting the precision of effectiveness estimates and amplifying the uncertainty in the head-to-head comparison between the 2 drugs (**Figure 1**). This analysis examined the effect of alirocumab therapy only among patients with a history of MI in the preceding year. Therefore, our findings should not be extrapolated to patients with stable coronary heart disease, who typically have a lower baseline risk for MACE and are likely to receive a smaller absolute benefit.

In summary, because of our experience, we encourage other members of the academic community to become involved in evaluating the cost-effectiveness of new therapies in a timely manner. We believe that this involvement may positively influence the pricing and adoption of interventions that are useful to patients,

Figure 2. Effect of baseline cardiovascular risk and alirocumab price on the cost-effectiveness of alirocumab relative to a statin alone (*top*) or ezetimibe (*bottom*).

ICER of Statin + Alirocumab Compared With Statin Alone

Annual Cost of Alirocumab Therapy	Stable ASCVD (MACE Rate, 4.1 per 100 Patient-Years)	Recent MI With LDL-C Level ≥1.81 mmol/L* Despite Statin Therapy (MACE Rate, 6.2 per 100 Patient-Years)	Recent MI With LDL-C Level ≥2.59 mmol/L* Despite Statin Therapy (MACE Rate, 7.2 per 100 Patient-Years)
$14 560 (WAC, March 2018)	846 000	622 000	544 000
$7187 (U.S. price net of rebates and discounts, March 2018)	419 000	308 000	269 000
$2912 (80% discount from WAC)	172 000	126 000	110 000
$1456 (90% discount from WAC)	88 000	64 000	55 000

ICER of Statin + Alirocumab Compared With Statin + Ezetimibe

Annual Cost of Alirocumab Therapy	Stable ASCVD (MACE Rate, 4.1 per 100 Patient-Years)	Recent MI With Baseline LDL-C Level ≥1.81 mmol/L* Despite Statin Therapy (MACE Rate, 6.2 per 100 Patient-Years)	Recent MI With Baseline LDL-C Level ≥2.59 mmol/L* Despite Statin Therapy (MACE Rate, 7.2 per 100 Patient-Years)
$14 560 (WAC, March 2018)	3 090 000	2 267 000	1 992 000
$7187 (U.S. price net of rebates and discounts, March 2018)	1 360 000	997 000	876 000
$2912 (80% discount from WAC)	358 000	262 000	230 000
$1456 (90% discount from WAC)	88 000†	64 000†	55 000†

ICER >$150 000 per QALY gained
ICER ≤$150 000 but ≥$100 000 per QALY gained
ICER <$100 000 per QALY gained

In a hypothetical analysis, we assumed that alirocumab would produce a 15% reduction in MACE, defined as a composite of cardiovascular death, nonfatal MI, and nonfatal stroke. We then evaluated its cost-effectiveness among 3 subgroups defined by baseline risk of MACE: a lower-risk group with a baseline MACE rate of 4.1 per year, an intermediate-risk group with a baseline rate of 6.2 per year, and a higher-risk group with a baseline rate of 7.2 per year. These groups were chosen to approximate the MACE rates among patients with a history of stable ASCVD, those with a history of recent MI, and those with a history of recent MI and a baseline LDL-C level ≥2.59 mmol/L (≥100 mg/dL), respectively. In each subgroup, we evaluated the incremental cost-effectiveness of alirocumab at 4 price points: the March 2018 WAC of $14 560, the March 2018 mean U.S. price net of discounts and rebates of $7187, and hypothetical prices representing 80% and 90% discounts from the WAC ($2912 and $1456, respectively). In the top panel, statin plus alirocumab is compared with statin alone, whereas in the bottom panel, statin plus alirocumab is compared with statin plus ezetimibe. The figure shows that the ICER for alirocumab relative to the comparator improves steadily with increasing baseline risk (that is, the higher the baseline MACE risk, the greater the net benefit of alirocumab and hence the lower the ICER), but the cost-effectiveness threshold of $100 000 per QALY gained is not achieved even in the highest-risk group unless the price is reduced substantially. Targeting higher-risk groups would reduce the number of patients eligible for therapy and ameliorate the total budget impact of adopting this novel therapy, but unless this focus on a higher-risk population is complemented by a substantial reduction in drug price, achieving cost-effectiveness at conventional willingness-to-pay thresholds will not be possible. ASCVD = atherosclerotic cardiovascular disease; ICER = incremental cost-effectiveness ratio; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular events; MI = myocardial infarction; QALY = quality-adjusted life year; WAC = wholesale acquisition cost.

* To convert millimoles per liter to milligrams per deciliter, divide by 0.0259.

† At this price, the ICER for statin plus alirocumab relative to statin plus ezetimibe is less than the ICER for statin plus ezetimibe relative to a statin alone. Statin plus ezetimibe is therefore eliminated by extended dominance, and statin plus alirocumab is directly compared with a statin alone.

just as important clinical trials have the potential to influence clinical practice.

From Beth Israel Deaconess Medical Center, Boston, Massachusetts (D.S.K.); and University of California, San Francisco, San Francisco, California (J.P., P.G.C., D.G., P.C.W., K.B.).

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Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* The Cardiovascular Disease Policy Model is available to interested readers who submit a 1- to 2-page research proposal and collaboration plan to Dr. Bibbins-Domingo (e-mail, kirsten.bibbins-domingo@ucsf.edu) and sign the Creative Commons agreement available at http://tiny.ucsf.edu/CVDpolicymodel, pending approval by the model team. *Data set:* Data for this study come from sources detailed in the **Supplement** (available at Annals.org). Data from the Framingham Heart Study are available following approval of research applications submitted at http://biolincc.nhlbi.nih.gov/studies/framcohort/?q=framingham for the Framingham Heart Study cohort and http://biolincc.nhlbi.nih.gov/studies/framoffspring/?q=framingham for the Framingham Offspring Study. Data on the health survey, vital statistics, and health care costs are publicly available from government sources described in the **Supplement**.

Corresponding Author: Kirsten Bibbins-Domingo, PhD, MD, MAS, Department of Epidemiology and Biostatistics, University of California, San Francisco, 55 016th Street, 2nd Floor, Box 0560, San Francisco, CA 94143; e-mail, Kirsten.Bibbins-Domingo@ucsf.edu.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Kazi: Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, 375 Longwood Avenue, 4th Floor, Boston, MA 02215.
Ms. Penko, Drs. Coxson and Bibbins-Domingo, and Ms. Wei: Department of Epidemiology and Biostatistics, University of California, San Francisco, 55 016th Street, 2nd Floor, Box 0560, San Francisco, CA 94143.
Mr. Guzman: UCSF Center for Vulnerable Populations, 1001 Potrero Avenue, Building 10, W13, UCSF-ZSFGH Box 1364, San Francisco, CA 94110.

Author Contributions: Conception and design: D.S. Kazi, J. Penko, K. Bibbins-Domingo.
Analysis and interpretation of the data: D.S. Kazi, J. Penko, P.G. Coxson, D. Guzman, P.C. Wei, K. Bibbins-Domingo.
Drafting of the article: D.S. Kazi, K. Bibbins-Domingo.
Critical revision for important intellectual content: D.S. Kazi, J. Penko, K. Bibbins-Domingo.
Final approval of the article: D.S. Kazi, J. Penko, P.G. Coxson, D. Guzman, P.C. Wei, K. Bibbins-Domingo.
Provision of study materials or patients: D.S. Kazi, K. Bibbins-Domingo.
Statistical expertise: D.S. Kazi, K. Bibbins-Domingo.
Obtaining of funding: D.S. Kazi, K. Bibbins-Domingo.
Administrative, technical, or logistic support: J. Penko, P.C. Wei, K. Bibbins-Domingo.
Collection and assembly of data: D.S. Kazi, P.G. Coxson, K. Bibbins-Domingo.