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Cost-Effectiveness of Alirocumab in Patients With Acute Coronary Syndromes

The ODYSSEY OUTCOMES Trial

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ABSTRACT

BACKGROUND Cholesterol reduction with proprotein convertase subtilisin-kexin type 9 inhibitors reduces ischemic events; however, the cost-effectiveness in statin-treated patients with recent acute coronary syndrome remains uncertain.

OBJECTIVES This study sought to determine whether further cholesterol reduction with alirocumab would be cost-effective in patients with a recent acute coronary syndrome on optimal statin therapy.

METHODS A cost-effectiveness model leveraging patient-level data from ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) was developed to estimate costs and outcomes over a lifetime horizon. Patients (n = 18,924) had a recent acute coronary syndrome and were on high-intensity or maximum-tolerated statin therapy, with a baseline low-density lipoprotein cholesterol (LDL-C) level ≥70 mg/dl, non-high-density lipoprotein cholesterol ≥100 mg/dl, or apolipoprotein B ≥80 mg/l. Alirocumab 75 mg or placebo was administered subcutaneously every 2 weeks. Alirocumab was blindly titrated to 150 mg if LDL-C remained ≥50 mg/dl or switched to placebo if 2 consecutive LDL-C levels were <15 mg/dl. Incremental cost per quality-adjusted life-year (QALY) was determined with the addition of alirocumab versus placebo and, based on clinical efficacy findings from the trial, was stratified by baseline LDL-C levels ≥100 mg/dl and <100 mg/dl.

RESULTS Across the overall population recruited to the ODYSSEY OUTCOMES trial, using an annual treatment cost of US$5,850, the mean overall incremental cost-effectiveness ratio was US$92,200 per QALY (base case). The cost was US$41,800 per QALY in patients with baseline LDL-C ≥100 mg/dl, whereas in those with LDL-C <100 mg/dl the cost per QALY was US$299,400. Among patients with LDL-C ≥100 mg/dl, incremental cost-effectiveness ratios remained below US$100,000 per QALY across a wide variety of sensitivity analyses.

CONCLUSIONS In patients with a recent acute coronary syndrome on optimal statin therapy, alirocumab improves cardiovascular outcomes at costs considered intermediate value, with good value in patients with baseline LDL-C ≥100 mg/dl but less economic value with LDL-C <100 mg/dl. (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab [ODYSSEY OUTCOMES]; NCT01663402) (J Am Coll Cardiol 2020;75:2297-308) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CEAC = cost-effectiveness acceptability curve

CI = confidence interval

EQ-5D-3L = EuroQol 5-dimensional 3-level

HR = hazard ratio

ICER = incremental cost-effectiveness ratio

ITT = intention to treat

LDL-C = low-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin-kexin type 9

QALY = quality-adjusted life-year

WTP = willingness-to-pay

Potent reduction of low-density lipoprotein cholesterol (LDL-C) with proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibition improves cardiovascular outcomes in high-risk patients (1–3). Both the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) (1) and FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) (3) trials demonstrated a 15% relative risk reduction in their respective primary endpoints, with excellent safety and tolerability. Furthermore, in the ODYSSEY OUTCOMES trial, alirocumab, compared with placebo, when added to maximum-tolerated high-intensity statin therapy was associated with a 15% lower all-cause mortality (1,2).

ODYSSEY OUTCOMES demonstrated significant reductions in the occurrence of first ischemic events, and this effect was enhanced when total events were considered (4). Indeed, the total number of nonfatal cardiovascular events and deaths prevented by alirocumab was nearly twice the number of first events prevented. Despite evidence of substantial reductions in fatal and nonfatal events stemming from LDL-C lowering with PCSK9 inhibition, the cost of these monoclonal antibodies and associated administrative restrictions on their use have limited their uptake into clinical practice (5).

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Evidence on their cost-effectiveness versus other medical interventions in well-defined populations may help to align access to these therapies with their incremental value. Several cost-effectiveness analyses have been conducted to better ascertain value (6–12). The first 2 modeled treatment benefit without using any data from FOURIER or ODYSSEY OUTCOMES (6,8). Subsequent analyses used data from either FOURIER (7,9–11) or ODYSSEY OUTCOMES (12);

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Dr. Bhatt has served on the Advisory Boards of Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLx Pharma, and Regado Biosciences; has served on the Boards of Directors of Boston Veteran Affairs Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; has chaired the American Heart Association Quality Oversight Committee; has served on the Data Monitoring Committees of Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo), and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org; vice-chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Medtelligence/ReachMD (Continuing Medical Education Steering Committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and U.S. national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (Continuing Medical Education Steering Committees), *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); has received research funding from Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as a site coinvestigator for Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), and Svelte; has served as a trustee of American College of Cardiology; and has performed unfunded research for FlowCo, Merck, Novo Nordisk, and Takeda. 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however, all analyses used a Markov-based approach, which relied heavily on aggregate trial data and assumptions from outside the trial and only 1 analysis (11) utilized the lower list price. Thus, these models have not provided compelling economic support for this drug class. To evaluate how the recent evolution in pricing and a different modeling approach affect the estimated long-term cost-effectiveness

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of alirocumab, we undertook a trial-based cost-effectiveness analysis using ODYSSEY OUTCOMES patient-level data from the perspective of a U.S. private payer.

METHODS

PATIENT POPULATION. The ODYSSEY OUTCOMES trial design has been described (13). Briefly, the study enrolled 18,924 patients 1 to 12 months post-acute coronary syndrome (ACS) to evaluate the cardiovascular efficacy and safety of adding alirocumab to high-intensity or maximum-tolerated doses of statins. Patients were ≥40 years of age, had provided written informed consent, been hospitalized with ACS 1 to 12 months before randomization, and had LDL-C levels ≥70 mg/dl (1.81 mmol/l) or non-high-density lipoprotein cholesterol levels ≥100 mg/dl (2.59 mmol/l) or apolipoprotein B levels ≥80 mg/dl after ≥2 weeks of stable treatment with atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or the maximum tolerated dose of one of these statins. After a pre-randomization run-in phase, patients were randomly assigned (1:1) to blinded treatment with alirocumab 75 mg or matching placebo, given by subcutaneous injection every 2 weeks (see Supplemental Methods). The patients were followed for a median of 2.8 years (interquartile range: 2.3 to 3.4 years).

COST-EFFECTIVENESS MODEL STRUCTURE. Unlike previous cost-effectiveness analyses, which used Markov models (6–12), a trial-based model utilizing patient-level data from ODYSSEY OUTCOMES was developed to model costs and outcomes over a lifetime horizon. Supplemental Figure 1 presents the inputs and outputs of the ODYSSEY OUTCOMES-based cost-effectiveness model. In the base-case analysis, we used the intention-to-treat (ITT) population and the impact on all-cause death observed from the trial. Cardiovascular events of interest were fatal and nonfatal myocardial infarction, nonfatal ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization. Death was modeled separately to avoid double counting events.

SURVIVAL AND EVENT RATE EXTRAPOLATION. To extrapolate life expectancy using within-trial data, the survival probability for patients in the placebo arm was estimated using methods described by Nelson et al. (14). With this approach, the cumulative hazard function for all-cause death was estimated from the trial using a left-truncated and right-censored age-time scale based on a Cox proportional hazards model. With this age-based model that incorporates observed survival across ages of patients represented in the trial, a fourth order of age polynomial was fitted as reference survival probability. Life expectancy for each patient in the placebo arm of the trial was extrapolated with this model, accounting for the following baseline covariates: hypertension; anxiety; time from ACS event to randomization; diabetes; and sex. To reduce prolonged survival probabilities beyond age 80 years, a Gompertz model (a 2-parameter exponential death acceleration function suggested by Nelson et al. [14]) was used wherein the acceleration factor was consistent with that of Nelson et al. (14), doubling the death rate every 8 years after 80 years of age. To estimate survival for the alirocumab arm, the observed hazard ratio (HR) for all-cause death between alirocumab and placebo was applied to the extrapolated survival probability for the placebo group.

TABLE 1 Estimated Annual Health-Care Costs

Event	Cost (±10%)
Cardiovascular death	20,225 (18,203–22,248)
Nonfatal myocardial infarction (without revascularization)	18,682 (16,814–20,550)
Nonfatal ischemic stroke	12,617 (11,355–13,879)
Ischemia-driven revascularization or unstable angina requiring hospitalization	39,531 (35,578–43,484)

Costs are expressed in 2018 U.S. dollars.

Event rates per 100 patient-years, including total events, for nonfatal myocardial infarction, nonfatal ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization were estimated based on the trial data for each treatment group. Rates of nonfatal cardiovascular events observed in ODYSSEY OUTCOMES in each treatment arm throughout the follow-up period were assumed to be constant over the remaining life span of the patients.

HEALTH CARE RESOURCE USE AND COSTS. Fatal and nonfatal cardiovascular events were mapped to Medicare Diagnostic-Related Group codes by a panel of nosologists. Mean Medicare Diagnostic-Related Group payments from 2015 were used to calculate a payment, weighted by each cardiovascular event type (15), and updated to 2018 U.S. dollars using annual rate increases published by the Centers for Medicare and Medicaid Services (16). As Medicare reimbursement rates are considerably lower than commercial rates, we applied an inflation factor (1.88×) to patients under 65 years of age (73.5%) to better reflect payment for a commercial population. Mean inpatient payments for cardiovascular death, nonfatal

myocardial infarction, nonfatal ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization, are shown in Table 1.

The following algorithm was followed to ensure we did not double count costs of cardiovascular events: if a nonfatal myocardial infarction and an urgent revascularization occurred on the same day, only the cost of the revascularization was counted. Likewise, if any cardiovascular event occurred on the same day as a cardiovascular death, only cardiovascular death was counted. If a fatal myocardial infarction and an urgent revascularization occurred on the same day, the model only accounted for cardiovascular death; if the revascularization occurred on a different day, both were counted. Otherwise all events were assigned corresponding weighted-average payments to estimate inpatient costs.

The annual cost of alirocumab was assumed to be $5,850, reflective of the current list price not inclusive of any potential rebates/discounts offered to payers. An adherence rate was applied using the mean number of injections per year observed in the trial (21.8, 95% confidence interval [CI]: 21.7 to 22.0) divided by the 26 injections expected per year. Use of alirocumab was assumed to continue at this rate over the remaining life span of the patient, without accounting for future price reductions after loss of patent protection.

UTILITY ANALYSIS. The EuroQol 5-dimensional 3-level (EQ-5D-3L) instrument (17), a generic preference-based measure of health, was used to assess each patient's health status at baseline, every 2 to 4 months during the double-blind trial period, and on trial termination. Responses to the 5 items included in the EQ-5D-3L were converted to a utility tariff score using the U.S. scoring algorithm reported by Shaw et al. (18). A repeated-measures, mixed-effects model (19) was used to regress utility values on 4 major cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization) to estimate post-event decrements in EQ-5D-3L utility values. Each of the 4 major cardiovascular events was modeled using 2 indicator variables: acute phase and long-term phase. The acute phase indicated a cardiovascular event that occurred within 90 days before the assessment of EQ-5D-3L; the long-term phase indicated a cardiovascular event that occurred more than 90 days before the assessment. The EQ-5D-3L model also controlled for age, sex, baseline EQ-5D-3L utility, cardiovascular history, and diabetes at baseline. When modeling health utilities over time, the mean age-adjusted utility values were reduced by the acute-phase disutilities estimated in the regression model for nonfatal myocardial infarction, nonfatal ischemic stroke, unstable angina requiring hospitalization, and coronary revascularization, followed by chronic phase disutilities for each event until death.

COST-EFFECTIVENESS ANALYSIS. Quality-adjusted life-years (QALYs) and life-years gained were calculated for each year, accounting for the percentages of patients to have died or to have had each type of cardiovascular event in the current year, and the percentages with a history of cardiovascular events. Fatal events were assumed to have occurred half-way through the year. Acute-phase disutility weights were applied to a quarter of the year in which cardiovascular events occurred, and chronic-phase disutility weights were applied thereafter. After discounting, QALYs across all years were summed for each treatment group. The primary analysis was the incremental cost-effectiveness ratio (ICER), defined as the difference between mean discounted lifetime costs divided by the difference in mean discounted QALYs between the 2 treatment groups (i.e., alirocumab – placebo). Additionally, we estimated the annual cost of alirocumab necessary for it to become cost-effective at a commonly used willingness-to-pay (WTP) threshold (i.e., $100,000 per QALY) (20). Costs and QALYs were discounted at 3% per year (20).

COST-EFFECTIVENESS ACCEPTABILITY CURVES. The variability of the estimation for ICERs in the base-case analysis and sensitivity analyses were assessed by nonparametric bootstrapping with 10,000 replications (21). In each bootstrap sample, patients were randomly selected, with replacement within each treatment group; the full sequence of analyses described herein was executed. The percentages of bootstrap replications falling below a range of WTP thresholds were computed and plotted as cost-effectiveness acceptability curves (CEACs). The 2.5 and 97.5 percentiles of the bootstrap distribution provided the 95% confidence intervals for the ICERs.

SUBGROUP ANALYSIS. Post hoc analysis of ODYSSEY OUTCOMES revealed a significant statistical interaction between treatment with alirocumab and baseline levels of LDL-C <100 mg/dl versus ≥100 mg/dl for major adverse cardiovascular events and total nonfatal cardiovascular events and a trend for all-cause death ($p = 0.048$, $p = 0.026$, and $p = 0.057$, respectively) (Supplemental Methods). Considering interest among health care payers in the United States in identifying patients most likely to benefit from higher-cost treatments, stratified results are presented for patients with baseline LDL-C levels <100 mg/dl and ≥100 mg/dl.

TABLE 2 Model Input Parameters

Treatment Effect of Alirocumab			
	HR (95% CI)		
Event	ITT Population (Base Case)	Subgroup With LDL-C ≥100 mg/dl at Baseline	Subgroup With LDL-C <100 mg/dl at Baseline
Cardiovascular death	0.88 (0.74 to 1.05)	0.68 (0.52 to 0.90)	1.03 (0.82 to 1.29)
All-cause death	0.85 (0.73 to 0.98)	0.70 (0.55 to 0.88)	0.95 (0.79 to 1.14)

Event Rates (Per 100 Patient-Years) for Base-Case (ITT Population)		
	Rate (95% CI)	
Event	Alirocumab	Placebo
All-cause death	1.24 (1.11 to 1.37)	1.46 (1.32 to 1.60)
Cardiovascular death	0.89 (0.78 to 1.00)	1.01 (0.89 to 1.13)
Nonfatal MI for disutility*	3.20 (2.91 to 3.50)	3.69 (3.39 to 4.01)
Nonfatal MI for cost*	2.70 (2.43 to 2.98)	3.12 (2.84 to 3.41)
Nonfatal ischemic stroke	0.44 (0.36 to 0.53)	0.62 (0.52 to 0.73)
Unstable angina requiring hospitalization	0.14 (0.09 to 0.19)	0.24 (0.18 to 0.30)
Ischemia-driven revascularization	3.19 (2.95 to 3.45)	3.70 (3.43 to 3.97)

Utility Analyses for the Base Case (ITT Population)		
Analysis	Time Frame	Mean (95% CI)
Utilities		
Baseline		0.893 (0.891 to 0.895)
Age		−0.0005 (−0.001 to 0.000)
Disutilities (acute or long term)		
Nonfatal MI	Acute†	−0.028 (−0.034 to −0.021)
	Long term‡	−0.023 (−0.027 to −0.018)
Nonfatal ischemic stroke	Acute†	−0.073 (−0.090 to −0.056)
	Long term‡	−0.069 (−0.080 to −0.059)
Unstable angina requiring hospitalization	Acute†	−0.021 (−0.045 to 0.003)
	Long term‡	−0.001 (−0.016 to 0.014)
Ischemia-driven revascularization	Acute†	−0.007 (−0.014 to −0.001)
	Long term‡	0.002 (−0.002 to 0.007)

*Event rate differs to avoid double-counting of events. †Event occurring within 90 days. ‡Event occurring after 90 days.
CI = confidence interval; HR = hazard ratio; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

SENSITIVITY ANALYSES. Several sensitivity analyses were performed to evaluate the impact on ICERs when applying alternative assumptions to estimate expected survival. In 1 sensitivity analysis, the HR for the effect of alirocumab on cardiovascular death (HR: 0.88; 95% CI: 0.74 to 1.05, for the ITT population) was applied instead of the effect of alirocumab on all-cause death (base case), whereby the effect of alirocumab was applied to cardiovascular deaths, whereas no treatment effect was applied to the noncardiovascular death rate. The proportions of cardiovascular to all deaths in the first 2 years were based on the placebo group in ODYSSEY OUTCOMES (first year is 78% and second year is 67%). The proportion of all deaths attributed to cardiovascular causes at 3 years and beyond (65%) was applied to all subsequent years.

Evidence for a 1-year delay in the beneficial treatment effect of LDL-C lowering has been demonstrated in randomized trials (3,22,23). Therefore, an additional sensitivity analysis, which evaluated the impact of alirocumab by applying separate HRs for mortality and nonfatal cardiovascular events in the first year of treatment and beyond the first year of follow-up in ODYSSEY OUTCOMES, was undertaken.

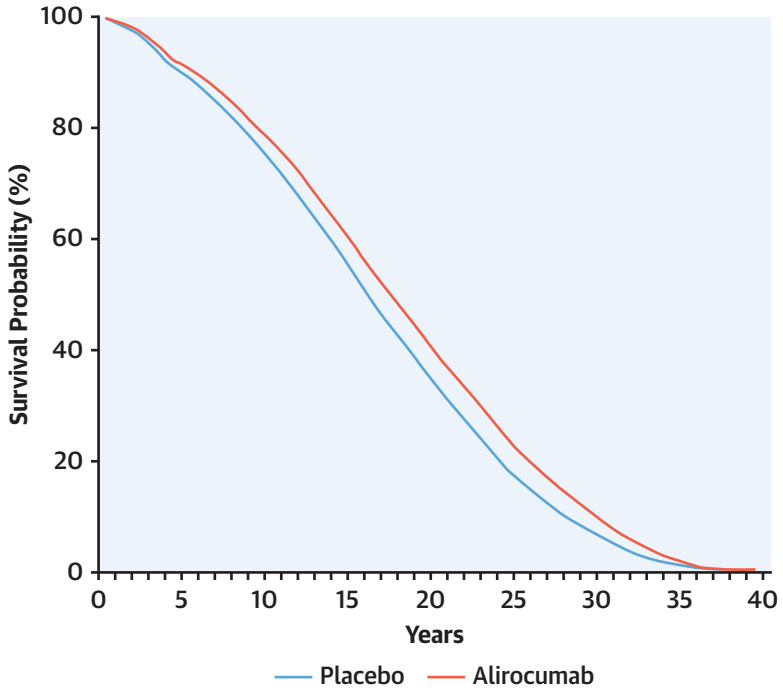
One-way sensitivity analyses were performed using alternate values for model parameters to identify key model drivers and the influence of parameter uncertainty: cardiovascular event costs (±10%); range of utilities/disutilities (95% CIs); HRs for death and nonfatal cardiovascular event rates in the placebo arm (95% CIs).

All analyses were conducted in SAS (version 9.4, SAS Software, Cary, North Carolina) and Excel (version 2010, Microsoft, Redmond, Washington).

RESULTS

Demographic and clinical characteristics of the population have been described (1). The flow chart is shown in Supplemental Figure 2. Briefly, the mean

FIGURE 1 Extrapolated Survival Curves by Treatment



Life expectancy was extrapolated using within-trial data. The survival probability for patients in the placebo arm was estimated using the cumulative hazard function for all-cause death, estimated from the trial based on a Cox proportional hazards model. To reduce prolonged survival probabilities beyond 80 years of age, a Gompertz model (a 2-parameter exponential death acceleration function) was used. To estimate survival for the alirocumab arm, the observed hazard ratio for all-cause death between alirocumab versus placebo was applied to the extrapolated survival probability for the placebo group.

age was 59 ± 9 years, 75% (n = 14,162) were men, and 79% (n = 15,024) were white. Mean baseline LDL-C was 92 ± 31 mg/dl, with 89% receiving a high-intensity statin at the time of randomization.

BASE-CASE ANALYSES. Survival extrapolation and cardiovascular event rates. Based on the method of Nelson et al. (14), the average life expectancy of the placebo group was 75.28 years (range 41.36 to 94.72 years). After applying the observed average HR of 0.85 (95% CI: 0.73 to 0.98) (**Table 2**), representing the impact of alirocumab on the rate of all-cause death from the ITT population for the base-case analysis, the extrapolated survival probabilities over life-year are illustrated in **Figure 1**, giving a life expectancy for alirocumab of 76.56 years. The remaining years of survival (undiscounted) were estimated at 17.32 (95% CI: 16.38 to 18.35) with alirocumab and 16.06 (95% CI: 15.52 to 16.61) with placebo based on the area under the survival curves. The discounted mean life-years were 13.07 (95% CI: 12.53 to 13.65) years in the alirocumab arm versus 12.33 (95% CI: 12.00 to 12.66) years in the placebo arm (Supplemental Table 1). Further validation details for the model are provided in the Supplemental Methods and Supplemental Figures 3 to 5. **Table 2** displays the rates for cardiovascular events per 100 patient-years in the 2 treatment arms estimated from the trial for the ITT population.

UTILITY ANALYSIS. **Table 2** reports the results of the mixed-effects regression analyses, showing the estimated short-term and long-term impacts of total nonfatal events on EQ-5D-3L health-utility weights in the trial. After applying the disutility weights to the extrapolated survival curves, the discounted mean QALYs were 11.53 years in the alirocumab arm versus 10.87 years in the placebo arm, resulting in a difference of 0.66 gained QALYs in the alirocumab group in the base-case analysis.

OVERALL AND STRATIFIED COST-EFFECTIVENESS. In the base-case analysis, discounted lifetime costs per patient in the alirocumab and placebo groups were $97,400 and $36,100, respectively, representing an increase of $61,300 with the addition of alirocumab to background statin therapy. When accounting for a

TABLE 3 Base-Case Cost-Effectiveness Results

	Lifetime Cost ($)	Incremental Difference ($)	LY	Incremental Difference	QALY Gained	Incremental Difference	ICER ($/LY Gained)	ICER ($/QALY)	VBP at $100,000/QALY
Base case									
Alirocumab	97,400 (93,500 to 101,400)	61,300 (57,100 to 65,700)	13.07 (12.52 to 13.66)	0.74 (0.09 to 1.43)	11.53 (11.05 to 12.05)	0.66 (0.09 to 1.26)	82,400 (42,400 to 396,500)	92,200 (48,700 to 418,700)	6,319
Placebo	36,100 (34,000 to 38,200)		12.33 (12.00 to 12.65)		10.87 (10.58 to 11.16)				
LDL-C ≥100 mg/dl subgroup									
Alirocumab	105,700 (98,500 to 113,700)	61,500 (53,500 to 70,200)	13.23 (12.31 to 14.26)	1.68 (0.58 to 2.83)	11.50 (10.71 to 12.38)	1.47 (0.53 to 2.45)	36,600 (23,600 to 94,200)	41,800 (27,200 to 103,700)	13,357
Placebo	44,100 (40,100 to 48,200)		11.55 (11.01 to 12.12)		10.03 (9.56 to 10.53)				
LDL-C <100 mg/dl subgroup									
Alirocumab	87,000 (82,400 to 91,900)	60,500 (55,700 to 65,700)	12.90 (12.20 to 13.63)	0.22 (−0.58 to 1.05)	11.45 (10.84 to 12.09)	0.20 (−0.50 to 0.93)	274,000 (−2,069,800 to 1,921,400)	299,400 (−2,312,200 to 2,347,000)	2,083
Placebo	26,500 (24,500 to 28,600)		12.68 (12.27 to 13.08)		11.25 (10.88 to 11.60)				

Parenthetical values are 95% CI. Costs are expressed in 2018 U.S. dollars and are rounded to nearest $100.
ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; VBP = value-based pricing; other abbreviations as in Table 2.

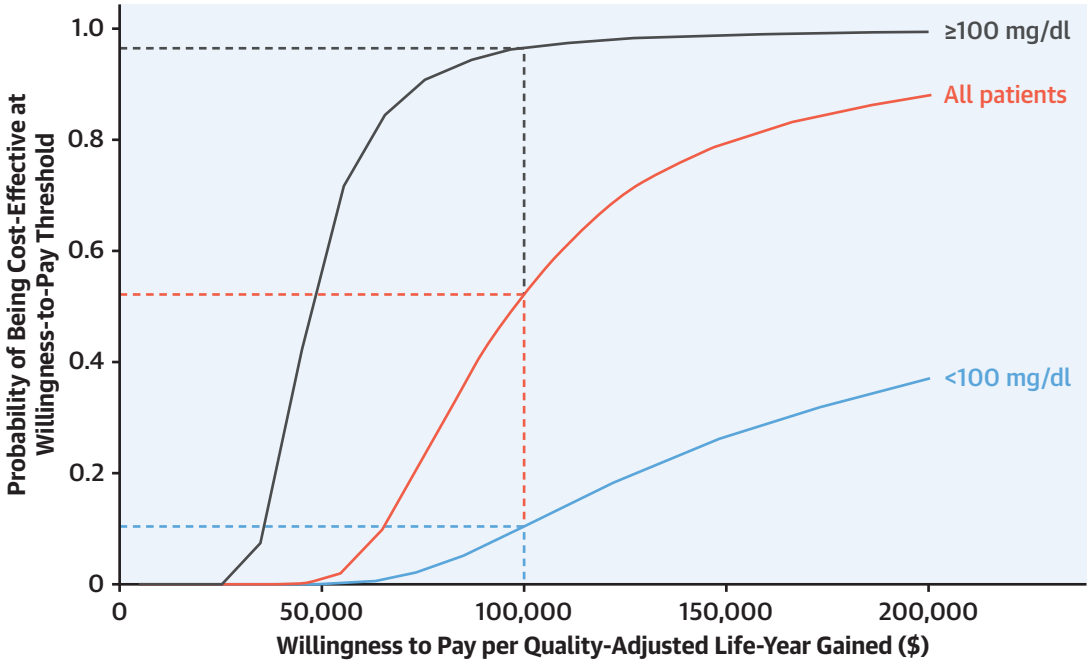
0.66 gain in QALYs with alirocumab versus placebo, the ICER was estimated at $92,200 per QALY gained (**Table 3**). At the $100,000 WTP threshold, the annual value-based price for alirocumab was up to $6,319. The CEAC revealed that 57.8% of replicates fell at or below a $100,000 per QALY WTP threshold and 81.7% fell at or below a $150,000 per QALY threshold (**Central Illustration**). Event rates and utility values for patients with a baseline LDL-C ≥100 mg/dl and those with a value <100 mg/dl are shown in Supplemental Tables 2 and 3. If alirocumab treatment was restricted to patients with a baseline LDL-C ≥100 mg/dl, the incremental cost was $61,500 with an incremental QALY of 1.47, leading to an ICER of $41,800 per QALY gained. In patients with a baseline LDL-C <100 mg/dl, the incremental cost was $60,500 with an incremental QALY of 0.20, leading to an ICER of $299,400 (Supplemental Table 4). The CEACs show that 97.1% of replicates fell at or below the $100,000 per QALY WTP threshold for the ≥100 mg/dl subgroup, and 12.4% for the <100 mg/dl subgroup (**Central Illustration**).

SENSITIVITY ANALYSES. Input parameters for other sensitivity analyses are reported in Supplemental Table 5. When cardiovascular death was used in lieu of all-cause death, the ICER increased to $173,800 per QALY gained in the ITT population and $53,800 per QALY gained in the ≥100 mg/dl subgroup. For mortality and nonfatal cardiovascular events, when we applied separate HRs in the first year of treatment and beyond the first year of follow-up, the ICER decreased to $66,600 per QALY in the ITT population (Supplemental Table 6). The CEAC for the varying HR from the ITT population is shown in Supplemental Figure 6 and for the cardiovascular HR in Supplemental Figure 7. One-way sensitivity analyses, performed using alternate values for model parameters, showed that the main driver was the mortality HR, whereas the utility, nonfatal cardiovascular event rates, and cardiovascular event costs had limited impact on the ICER (Supplemental Figure 8).

DISCUSSION

Using patient-level data from the ODYSSEY OUTCOMES trial, we extrapolated observed survival to determine the cost-effectiveness of alirocumab. In our base-case analysis, the ICER was $92,200 per QALY, which is considered as intermediate value as defined in the American Heart Association/American College of Cardiology guidelines. However, this figure masks important differences in cost-effectiveness among patients with a baseline LDL-C above or below 100 mg/dl. Among patients with a baseline LDL-C ≥100 mg/dl, the ICER was more attractive, at $41,800 per QALY. This amount is below the $50,000 per QALY benchmark suggested by American Heart Association/American College of Cardiology to confer “high value” for high-income countries (24). When additional analyses were conducted using the treatment effect for cardiovascular death in lieu of all-cause death, the results were consistent, with an ICER of $53,800 for patients with a baseline LDL-C ≥100 mg/dl. On the other hand, in patients with a baseline LDL-C <100 mg/dl, alirocumab use resulted in an ICER of

CENTRAL ILLUSTRATION **Cost-Effectiveness Acceptability Curves (Intention-to-Treat Population) for the Base Case (Overall Hazard Ratio) and Low-Density Lipoprotein Cholesterol ≥100 mg/dl and <100 mg/dl Subgroups**



Bhatt, D.L. et al. J Am Coll Cardiol. 2020;75(18):2297–308.

Cost-effectiveness acceptability curves (CEACs) summarize the impact of uncertainty on the result of an economic evaluation. The variability of the estimation for incremental cost-effectiveness ratios in the base-case analysis was assessed by nonparametric bootstrapping with 10,000 replications. The y-axis is the probability of being cost-effective at any willingness-to-pay threshold (WTP) (x-axis). For example, for all patients in the trial, at the $100,000 WTP threshold, alirocumab would be cost-effective at a price of $6,319 58% of the time. If the threshold was $150,000, alirocumab would be cost-effective 82% of the time.

$299,400 per QALY, which would be considered low value (corresponding value-based prices at different costs/QALYs are shown in Supplemental Table 7).

In the subgroup with LDL-C ≥100 mg/dl at baseline, in which alirocumab appeared to demonstrate good value, there is biological plausibility for its increased value for money (1,2,25). Baseline risk in these patients is generally higher than among patients with LDL-C <100 mg/dl. At the same time, a higher LDL-C concentration at baseline is associated with a larger absolute decrease in LDL-C under treatment with alirocumab, yielding a greater effect on risk reduction. Together, these findings make the subgroup with baseline LDL-C ≥100 mg/dl clinically relevant and easily identified in routine clinical practice. Although we did not calculate cost effectiveness in other subgroups, favorable value for money with alirocumab treatment might also be expected in other patient categories defined by high absolute risk of recurrent ischemic events and death and large absolute benefit from treatment. Among such subgroups identified in the ODYSSEY OUTCOMES trial are those with diabetes, polyvascular disease, prior coronary artery bypass surgery, or high levels of lipoprotein(a) (26–29).

The current study is a trial-based analysis that uses patient-level data obtained directly from the trial. Our study differs from prior cost-effectiveness analyses of PCSK9 inhibition that utilized a Markov transition-based model, which relies on aggregate data from the trials (7,9–12). All model inputs for the current study were obtained from ODYSSEY OUTCOMES, whereas the prior analyses relied on data inputs from outside the trial, such as background event rates, treatment effect, and utility parameters. Patient-level data provide further insights. For one, we can account for patient characteristics associated with mortality that would not be evident with trial-level results. For instance, for a given mortality rate, if younger patients more often died in the trial, there

would be a greater reduction in life expectancy than if older patients had died. There would be no way to incorporate (or know) that from trial-level data. Generally, using patient-level data facilitates subgroup analyses because they inherently incorporate relationships between patient characteristics and rates of nonfatal events, mortality, and disutilities that would not be accounted for in a trial-level analysis that may just change the HR for the treatment effect in the corresponding subgroup. Given the emphasis on cost-effectiveness in the 2018 U.S. cholesterol-lowering guidelines (24), the present approach may provide a useful tool for clinicians to decide when to use a PCSK9 inhibitor after ACS.

Apart from the price of treatment, the 2 main "drivers" of value are the background event rate and survival benefit. In cardiovascular outcomes trials, the latter ordinarily is the more important factor (30). Some prior PCSK9 inhibitor cost-effectiveness analyses have either underestimated the background cardiovascular event rate in the everyday clinical practice or do not take into consideration the benefits of averting death (7,12). With a very high-risk population and longer duration of follow-up than previous trials of PCSK9 inhibitors, fewer deaths were observed with alirocumab than with placebo in the ODYSSEY OUTCOMES trial. The trial therefore provides a relevant dataset to project the effect of PCSK9 inhibition after ACS on long-term survival and cost per QALY.

A limitation in previous models is the way death was modeled. For example, 2 prior analyses (10,12) used the cardiovascular disease policy model to determine the cost-effectiveness of alirocumab or evolocumab based on overall trial hazard ratios for selected endpoints. Rather than giving "credit" for averting death by applying trial-specific HRs for that endpoint, Kazi et al. (12) stated that all-cause mortality was mediated through a reduction in the risk of death related to coronary heart disease and stroke. For alirocumab, the assumed HR applied to account for death was not the HR noted in the trial (0.85); rather, an HR of 0.88 was used, which was the stated HR for a major coronary heart disease event. In the FOURIER trial, which tested PCSK9 inhibition with evolocumab in patients with chronic atherosclerotic cardiovascular disease, the HR (evolocumab/placebo) for all-cause death was 1.05. In a cost-effectiveness analysis of that trial, the HR for myocardial infarction was used to project a long-term effect on death even though no mortality benefit was observed during the trial (12). A time-varying HR of 0.80 for the first year of treatment and 0.65 for the remaining period of a patient's life was assumed, resulting in a value-based price of $4,200 per year for evolocumab. This analysis was recently updated, incorporating the 60% reduction in the annual U.S. list price from $14,523 to $5,850 to the previous model. It also focused on patients with very high-risk atherosclerotic cardiovascular disease (defined by the new U.S. guidelines) and high baseline cardiovascular event rate assumptions, concluding that evolocumab is cost-effective in very high-risk patients (11). Additionally, previous models did not consider all payer-relevant endpoints, such as coronary revascularization, which entails a high cost.

STUDY LIMITATIONS. Potential limitations of this analysis include some of the assumptions in our model. We did not use country-specific data, but rather applied U.S. costs to the global population enrolled in ODYSSEY OUTCOMES. The treatment effect of alirocumab was applied to all-cause mortality, which in the overall trial was nominally but not formally statistically significant according to pre-specified hierarchical testing. However, in the subgroup of patients with LDL-C ≥100 mg/dl, the signal for mortality reduction was amplified and was corroborated by a significant reduction in cardiovascular mortality. The median follow-up in the trial was 2.8 years, though, by necessity, we extrapolated to (remaining) lifetime survival and costs. We did not consider follow-up or outpatient costs stemming from nonfatal cardiovascular events (e.g., those associated with recurrent hospitalization, rehabilitation, other medications, and lost years of employment). Time from index ACS to the beginning of randomization was incorporated as a covariate in the Nelson et al. model (14); based on our model, we could not examine whether alirocumab would be cost effective by delaying treatment. The disutilities in our trial were of lower magnitude than those applied in other publications (19), likely due to the missing EQ-5D-3L assessments during the acute phase of events. Our estimates include only the list price of alirocumab and do not consider discounts usually offered to payers. Finally, aside from our LDL-C subgroups, we did not incorporate other important subgroups, which could have higher baseline cardiovascular risk. In these respects, the present results provide a conservative estimate of the cost-effectiveness of alirocumab after ACS.

CONCLUSIONS

In a non-pre-specified subgroup analysis, we found that at an annual list price of $5,850, alirocumab represents good value for money in patients with ACS and baseline LDL-C ≥100 mg/dl despite statin therapy, though less value in patients with LDL-C <100 mg/dl.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Patient-level health economic analysis suggests that to optimize value in relation to cost PCSK9 inhibitor therapy should be directed toward patients at highest risk, such as those with baseline LDL-C levels ≥100 mg/dl.

TRANSLATIONAL OUTLOOK: Additional cost-effective strategies that reduce LDL-C and lower the risk of ischemic events and death are needed for patients in whom statin therapy is not sufficient.

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KEY WORDS acute coronary syndromes, alirocumab, cholesterol, cost-effectiveness, economic analysis

APPENDIX For supplemental methods, figures, tables, and a list of ODYSSEY OUTCOMES committee members, investigators, and contributors, please see the online version of this paper.