



Original Investigation | Cardiology

Cost-effectiveness of Icosapent Ethyl for High-risk Patients With Hypertriglyceridemia Despite Statin Treatment

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Abstract

IMPORTANCE The Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT) demonstrated the efficacy of icosapent ethyl (IPE) for high-risk patients with hypertriglyceridemia and known cardiovascular disease or diabetes and at least 1 other risk factor who were treated with statins.

OBJECTIVE To estimate the cost-effectiveness of IPE compared with standard care for high-risk patients with hypertriglyceridemia despite statin treatment.

DESIGN, SETTING, AND PARTICIPANTS An in-trial cost-effectiveness analysis was performed using patient-level study data from REDUCE-IT, and a lifetime analysis was performed using a microsimulation model and data from published literature. The study included 8179 patients with hypertriglyceridemia despite stable statin therapy recruited between November 21, 2011, and May 31, 2018. Analyses were performed from a US health care sector perspective. Statistical analysis was performed from March 1, 2018, to October 31, 2021.

INTERVENTIONS Patients were randomly assigned to IPE, 4 g/d, or placebo and were followed up for a median of 4.9 years (IQR, 3.5–5.3 years). The cost of IPE was \$4.16 per day after rebates using SSR Health net cost (SSR cost) and \$9.28 per day with wholesale acquisition cost (WAC).

MAIN OUTCOMES AND MEASURES Main outcomes were incremental quality-adjusted life-years (QALYs), total direct health care costs (2019 US dollars), and cost-effectiveness.

RESULTS A total of 4089 patients (2927 men [71.6%]; median age, 64.0 years [IQR, 57.0–69.0 years]) were randomly assigned to receive IPE, and 4090 patients (2895 men [70.8%]; median age, 64.0 years [IQR, 57.0–69.0 years]) were randomly assigned to receive standard care. Treatment with IPE yielded more QALYs than standard care both in trial (3.34 vs 3.27; mean difference, 0.07 [95% CI, 0.01–0.12]) and over a lifetime projection (10.59 vs 10.35; mean difference, 0.24 [95% CI, 0.15–0.33]). In-trial, total health care costs were higher with IPE using either SSR cost (\$18 786) or WAC (\$24 544) than with standard care (\$17 273; mean difference from SSR cost, \$1513 [95% CI, \$155–\$2870]; mean difference from WAC, \$7271 [95% CI, \$5911–\$8630]). Icosapent ethyl cost \$22 311 per QALY gained using SSR cost and \$107 218 per QALY gained using WAC. Over a lifetime, IPE was projected to be cost saving when using SSR cost (\$195 276) compared with standard care (\$197 064; mean difference, –\$1788 [95% CI, –\$9735 to \$6159]) but to have higher costs when using WAC (\$202 830) compared with standard care (mean difference, \$5766 [95% CI, \$1094–\$10 438]). Compared with standard care, IPE had a 58.4% lifetime probability of costing less and being more effective when using SSR cost and an 89.4% probability of costing less than \$50 000 per QALY

(continued)

Key Points

Question What is the cost-effectiveness of icosapent ethyl from a US health care perspective for high-risk patients with hypertriglyceridemia despite statin treatment?

Findings This economic evaluation including 8179 patients found that icosapent ethyl at a cost of \$4.16 to \$9.28 per day had a high probability of costing less than \$100 000 per quality-adjusted life-year gained. At the lower cost, treatment with icosapent ethyl may be a dominant strategy, offering better outcomes at lower cost.

Meaning This study suggests that, for high-risk patients with hypertriglyceridemia despite statin treatment, icosapent ethyl may be cost-effective at commonly accepted willingness-to-pay thresholds.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

gained when using SSR cost and a 72.5% probability of costing less than \$50 000 per QALY gained when using WAC.

CONCLUSIONS AND RELEVANCE This study suggests that, both in-trial and over the lifetime, IPE offers better cardiovascular outcomes than standard care in REDUCE-IT participants at common willingness-to-pay thresholds.

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Introduction

The Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) evaluated the efficacy of icosapent ethyl (IPE) in reducing cardiovascular events among high-risk patients with cardiovascular disease (CVD) or diabetes and another risk factor.^{1,2} For total primary events (first and subsequent), there was a 30% relative risk reduction from 89 to 61 events per 1000 patient years ($P < .001$) among those randomly assigned to receive IPE.³⁻⁶

Although REDUCE-IT demonstrated the efficacy and safety of IPE in reducing cardiovascular events among high-risk patients, whether these benefits provide good value (ie, is IPE worth what it costs?) has not been thoroughly explored. We conducted a cost-effectiveness study of REDUCE-IT participants to estimate the incremental in-trial and lifetime health gains, health care costs, and cost-effectiveness of adding IPE, 4 g/d, to statin therapy.

Methods

Study Design and Participants

The details of the REDUCE-IT design have been previously published.^{3,7,8} In brief, patients were randomized in a double-blinded manner to receive IPE, 4 g/d, or placebo between November 21, 2011, and May 31, 2018, at 473 sites in 11 countries. Eligible patients had statin-stabilized fasting triglyceride levels between 135 and 500 mg/dL (to convert to millimoles per liter, multiply by 0.0113) as well as low-density lipoprotein cholesterol levels between 40 and 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259). At enrollment, patients were required to be receiving statin therapy for 4 weeks or more. This study was conducted with institutional review board approval (for sites in North America, Advarra provided institutional review board approval and for sites outside North America, local institutional review boards provided approval). Patients provided written consent. The data supporting the findings of this study may be made available from the corresponding author on reasonable request. The present study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.^{9,10} Analyses were performed from a US health care sector perspective.¹⁰

Event Definition

The REDUCE-IT data set included patient-level baseline characteristics as well as all CVD and safety events recorded during the trial follow-up period (eTable 1 and eTable 2A in the [Supplement](#)).³ Events over the lifetime were modeled (eTable 2B in the [Supplement](#)). Patient-level events included nonfatal and fatal CVD, including myocardial infarction, stroke, and cardiac arrest; revascularization with percutaneous coronary intervention or coronary artery bypass grafting surgery; hospitalization for heart failure, atrial fibrillation, ventricular tachycardia, peripheral arterial disease requiring intervention, or unstable angina; and syncope and major bleeding. Other outcomes and serious adverse events that did not differ between the study groups were not included.

The REDUCE-IT Clinical Endpoint Committee charter prespecified handling conventions for specific event combinations.^{3,7,8} To avoid double costing of hospitalizations when closely timed events are likely to be within a single hospitalization, the handling of multiple events in this analysis varies from the charter, requiring 3 days' separation of time to classify events as separate events. When multiple events occurred within 3 days, the costlier event was included. Competing risk analysis, based on the cumulative incidence function, was applied to estimate the marginal probability of an event in the presence of competing events.¹¹

Estimation of Cost

Patient-level acute and chronic event rates and medication use data from REDUCE-IT were used to inform health care resource use. Event costs were taken from the National Inpatient Sample (eTable 3 and eTable 4 in the [Supplement](#)).^{12,13} Because the National Inpatient Sample does not include professional costs (eg, physician fees), they were estimated by percentage share.¹⁴ In addition, background costs adjusted for age were included for all patients plus additional costs of chronic care after myocardial infarction and stroke. Total background lifetime costs were estimated from the mean Medicare per-capita expenditure, stratified by age group. In 2014, the latest date with available data, the mean Medicare per-capita expenditure was \$9840 for men and \$9922 for women aged 65 to 84 years and was \$18 408 for men and \$17 017 for women aged 85 years or older.¹⁵ The cost of medications was sourced from SSR Health net cost (SSR cost), an estimate of the cost to the consumer after application of discounts and rebates, and, separately, RedBook wholesale acquisition cost (WAC).¹⁶ The SSR cost for IPE is \$4.16 per day, for an annual cost of \$1518; the WAC for IPE is \$9.28 per day, for an annual cost of \$3387. Costs were inflated to 2019 US dollars (USD) using the Personal Consumption Expenditure index.¹⁷ In-trial and lifetime costs were estimated as the sum of background health care costs plus the costs of events and medications.

Life Expectancy

The projection of life expectancy was based on a Markov disease simulation model, in which each surviving patient was assumed to face a continuing risk of death, with estimates based on the age-, sex-, and race- and ethnicity-specific risks of death obtained from US life tables calibrated to the observed 4.9-year mortality for the REDUCE-IT standard care group.¹⁸ The estimated and observed cumulative incidence and hazard ratios for cardiovascular events at the median follow-up period in REDUCE-IT were quantitatively compared to validate the model, including the estimated vs observed life-years lost, obtained by subtracting the survival times recorded in REDUCE-IT from estimated age- and sex-specific life expectancy estimates. Events and hospitalizations after the trial period were estimated by carrying forward the in-trial event rates and mortality in both groups of REDUCE-IT, with a multiplicative factor (multiplier) for event rates based on patient age group (eTable 5 in the [Supplement](#)).^{19,20} To evaluate the lifetime benefit associated with IPE, we carried forward the proportional hazard ratios from REDUCE-IT.

Quality-Adjusted Life-Years

We determined quality-adjusted life-years (QALYs) by multiplying survival, measured in life-years, by utility. Utility was estimated using disability weights from the Global Burden of Disease Study because it was not directly measured in REDUCE-IT.²¹⁻²³ Utility was determined by whether a patient experienced nonfatal cardiovascular events, revascularization procedures, or stroke. Utility values for chronic and acute disutility are included in eTable 6 in the [Supplement](#). As a base case, no pill-taking disutility was applied because taking pills has little or no association with utility for most patients,^{24,25} and daily pill-taking applies to both groups owing to the eligibility requirement of stable statin therapy.

Statistical Analysis

In-Trial Analysis

Statistical analysis was performed from March 1, 2018, to October 31, 2021. We assessed the distribution of incremental costs and QALYs from 5000 bootstrapped samples.²⁶ The cost-effectiveness of IPE was expressed as the incremental cost-effectiveness ratio (ICER) in cost per life-year or QALY gained for IPE compared with standard care. The ICER is not calculated when 1 strategy offers better outcome at lower cost (dominance).¹⁰ Future costs and QALYs were discounted 3% annually,²⁷ and the discontinuation rate was 6% based on the trial results (eFigure 1 in the [Supplement](#)). Icosapent ethyl was considered highly cost-effective if the ICER was less than \$50 000 per QALY gained and intermediate if it was between \$50 000 and \$150 000 per QALY gained.²⁸ Statistical analyses were performed using R, version 3.6.2 (R Group for Statistical Computing), Stata, version 16 (StataCorp LLC), and TreeAge Pro 2020, release 1.1 (TreeAge Software Inc).

Lifetime Analysis

Using Monte Carlo simulation, a Markov state-transition model (eFigure 2 in the [Supplement](#)) based on the 4.9-year median (IQR, 3.5-5.3 years) follow-up of in-trial patient-level data was used to extrapolate costs, life expectancy, and quality-adjusted life expectancy to estimate the ICER over a lifetime horizon.¹³ The simulation was run with half-year cycles. In each cycle, individuals could experience a fatal or nonfatal myocardial infarction, stroke, angina, or heart failure or could die of other causes. The results from REDUCE-IT were used to estimate the risk of death from all causes or CVD, CVD events, and serious adverse events in 10 000 hypothetical patients similar to patients in REDUCE-IT in terms of baseline characteristics. The transition probabilities for the simulation model are presented in eTable 7 in the [Supplement](#). Background mortality based on US life tables was integrated in the simulation model, accounting for the increased risk of death with age.¹⁸ Costs and QALYs after the first year of follow-up were discounted 3% annually.²⁷

Sensitivity Analyses

Threshold analyses, both in-trial and lifetime, examine the variation in daily cost of IPE for selected willingness-to-pay (WTP) thresholds over the lifetime. Input variable ranges for the sensitivity analyses are shown in eTable 8 in the [Supplement](#). The association of independently changing key variables across a plausible range of values with the ICER is shown in tornado diagrams. In addition, a lifetime probabilistic sensitivity analysis was conducted to assess the association with outcomes of simultaneous changes of all the variables involved.^{13,23,27,29} The model was run 5000 times, each taking random draws from prespecified uncertainty distributions of all model inputs.

Subgroup Analysis

All analyses were repeated in the following subgroups: age (≥ 65 vs < 65 years), sex, trial recruitment cohort (primary vs secondary prevention), baseline diabetes status, baseline serum triglyceride level (≥ 200 vs < 200 mg/dL and ≥ 150 vs < 150 mg/dL), and baseline low-density lipoprotein cholesterol level (≥ 70 vs < 70 mg/dL).

Scenario Analysis

To further examine the association with outcomes of CVD event costs, an alternative analysis was performed in which we used the Optum Research Database, a large database of commercially insured patients, for patients younger than 65 years and the Medicare Fee Schedule for patients aged 65 years or older (eTable 13 in the [Supplement](#)).³⁰⁻³² The Optum Research Database reflects commercial insurance and Medicare Advantage, but not Medicare fee-for-service; thus, only commercial enrollees were included. The Optum Research Database provides health care costs based on private payer claims, including insurer and patient payments for health care. Optum Research Database costs include professional costs (eg, physician fees). Medicare costs do not

include professional fees, so they were estimated by percentage share.¹⁴ All Optum Research Database and Medicare results are in the eResults, eTables 14-16, and eFigures 5-7 in the [Supplement](#).

Results

In REDUCE-IT, 4089 patients (2927 men [71.6%]; median age, 64.0 years [IQR, 57.0-69.0 years]) were randomly assigned to receive IPE, and 4090 patients (2895 men [70.8%]; median age, 64.0 years [IQR, 57.0-69.0 years]) were randomly assigned to receive standard care. The characteristics of the REDUCE-IT trial population are summarized in eTable 1 in the [Supplement](#). In-trial outcomes and costs are shown in eTable 2A in the [Supplement](#), and lifetime outcomes and costs are shown in eTable 2B in the [Supplement](#). The outcomes data for total events (first and subsequent) significantly favor IPE compared with standard care for cardiovascular death, nonfatal myocardial infarction with revascularization, nonfatal ischemic stroke, revascularization, peripheral arterial disease, and unstable angina. Nonfatal myocardial infarction without revascularization, hospitalization for atrial fibrillation or flutter, and major bleeding favor standard care. The Markov simulation model accurately regenerated the cumulative incidence curves and hazard ratios for the primary end point, key secondary end point, and additional end points and components during the 4.9-year follow-up period (eTable 9, eTable 10, and eFigure 3 in the [Supplement](#)).

In-Trial Analysis

With the use of the SSR cost, the cost of IPE was \$18 786, and the cost of standard care was \$17 273 (mean difference, \$1513 [95% CI, \$155-\$2870]); with the use of WAC, the cost of IPE was \$24 544, and the cost of standard care was \$17 273 (mean difference, \$7271 [95% CI, \$5911-\$8630]) (Table). Unadjusted life-years gained favored IPE vs standard care (4.31 vs 4.25; mean difference, 0.06 [95% CI, 0.00-0.12]). Adjusted for utility, patients treated with IPE accrued 3.34 QALYs vs those treated with standard care, who accrued 3.27 QALYs (mean difference, 0.07 [95% CI, 0.01-0.12]). The ICER point estimate was \$22 311 per QALY gained using SSR cost and \$107 218 per QALY gained using WAC. The cost-effectiveness scatterplots and acceptability curves show that, with the use of the SSR cost, patients treated with IPE had an ICER less than \$50 000 per QALY gained in 85.4% of simulations, an ICER less than \$100 000 per QALY gained in 95.2%, and an ICER less than \$150 000 per QALY gained in 97.1% (Figure 1). With the use of the WAC, patients treated with IPE had an ICER less than \$50 000 per QALY gained in 1.0% of simulations, an ICER less than \$100 000 per QALY gained in 42.7%, and an ICER less than \$150 000 per QALY gained in 74.5%.

Lifetime Analysis

With the use of the SSR cost, the cost of IPE was \$195 276, and the cost of standard care was \$197 064 (mean difference, -\$1788 [95% CI, -\$9735 to \$6159]); with the use of WAC, the cost of IPE was \$202 830, and the cost of standard care was \$197 064 (mean difference, \$5766 [95% CI, \$1094-\$10 438]) (Table). Unadjusted life-years gained favored IPE vs standard care (14.08 vs 13.94; mean difference, 0.16 [95% CI, 0.08-0.24]). Adjusted for utility, patients treated with IPE accrued 10.59 QALYs compared with those treated with standard care, who accrued 10.35 QALYs (mean difference, 0.24 [95% CI, 0.15-0.33]). The cost-effectiveness scatterplots and acceptability curves show that, with the use of SSR cost, patients treated with IPE had an ICER less than \$50 000 per QALY gained in 89.4% of simulations, an ICER less than \$100 000 per QALY gained in 98.9%, and an ICER less than \$150 000 per QALY gained in 99.9% (Figure 2). With the use of WAC, patients treated with IPE had an ICER less than \$50 000 per QALY gained in 72.5% of simulations, an ICER less than \$100 000 per QALY gained in 94.8%, and an ICER less than \$150 000 per QALY gained in 96.4%. Compared with standard care, IPE had a 58.4% lifetime probability of costing less and being more effective when using SSR cost, an 89.4% probability of costing less than \$50 000 per QALY gained when using SSR cost, and a 72.5% probability of costing less than \$50 000 per QALY gained when using WAC.

Threshold Analysis

In-trial and lifetime variation in the daily cost of IPE for selected WTP thresholds is shown in **Figure 3**. In-trial (Figure 3A), IPE is cost-effective at the \$50 000 threshold priced at or below \$5.84 per day. Over the lifetime (Figure 3B), IPE is dominant when priced at or below \$4.80 per day and cost-effective at the \$50 000 threshold priced at or below \$10.20 per day.

Sensitivity Analysis

Tornado diagrams show the univariate effect of varying key parameters associated with both effectiveness and cost (**Figure 4**). Both in-trial and over the lifetime, the ICER was primarily sensitive to the cost of IPE. Results of the lifetime probabilistic sensitivity analysis are shown in the Table as well as eFigure 4 in the **Supplement**. With the use of SSR cost, IPE was dominant compared with standard care in 47.6% of simulations and cost-effective in 86.2%, 96.9%, and 99.6% of simulations at the \$50 000, \$100 000, and \$150 000 WTP thresholds, respectively. With the use of WAC, IPE was a dominant strategy in 0.9% of simulations and cost-effective in 67.2%, 88.4%, and 94.6% of simulations at the \$50 000, \$100 000, and \$150 000 WTP thresholds, respectively.

Table. Cost-effectiveness Results for Icosapent Ethyl Compared With Standard Care Using National Inpatient Sample Costs

Variable	Mean total cost 2019, \$			Mean LYs or QALYs			ICER, USD/LY or USD/QALY, \$	%		Probability of cost-effectiveness, \$		
	IPE	SC	Δ (95% CI)	IPE	SC	Δ (95% CI)		IPE Dominant	IPE Dominated	<50 000	<100 000	<150 000
In-trial analysis												
LYs												
SSR	18 786	17 273	1513 (155 to 2870)	4.31	4.25	0.06 (0.00 to 0.12)	26 328	1.2	3.1	77.7	89.2	92.1
WAC	24 544	17 273	7271 (5911 to 8630)	4.31	4.25	0.06 (0.00 to 0.12)	126 524	0.0	2.7	0.0	31.1	60.3
QALYs												
SSR	18 786	17 273	1513 (155 to 2870)	3.34	3.27	0.07 (0.01 to 0.12)	22 311	1.5	0.9	85.4	95.2	97.1
WAC	24 544	17 273	7271 (5911 to 8630)	3.34	3.27	0.07 (0.01 to 0.12)	107 218	0.0	0.6	1.0	42.7	74.5
Lifetime model^a												
LYs												
SSR	195 276	197 064	-1788 (-9735 to 6159)	14.08	13.94	0.16 (0.08 to 0.24)	Dominant	69.7	<0.1	92.5	99.9	99.9
WAC	202 830	197 064	5766 (1094 to 10 438)	14.08	13.94	0.16 (0.08 to 0.24)	36 042	1.8	1.5	58.9	78.2	85.7
QALYs												
SSR	195 276	197 064	-1788 (-9735 to 6159)	10.59	10.35	0.24 (0.15 to 0.33)	Dominant	58.4	<0.1	89.4	98.9	99.9
WAC	202 830	197 064	5766 (1094 to 10 438)	10.59	10.35	0.24 (0.15 to 0.33)	23 866	1.2	0.6	72.5	94.8	96.4
Probabilistic sensitivity analysis												
LYs												
SSR	208 148	209 407	-1259 (-5136 to 3618)	14.10	13.96	0.14 (0.10 to 0.18)	Dominant	42.5	0.2	83.4	91.3	98.5
WAC	214 675	209 407	5268 (2784 to 7752)	14.10	13.96	0.14 (0.10 to 0.18)	37 751	1.9	2.2	56.1	76.8	91.7
QALYs												
SSR	208 148	209 407	-1259 (-5136 to 3618)	10.64	10.43	0.20 (0.18 to 0.22)	Dominant	47.6	0.1	86.2	96.9	99.6
WAC	214 675	209 407	5268 (2784 to 7752)	10.64	10.43	0.20 (0.18 to 0.22)	26 341	0.9	0.5	67.2	88.4	94.6

Abbreviations: Δ, difference between treatment with icosapent ethyl and standard care; ICER, incremental cost-effectiveness ratio; IPE, icosapent ethyl; LY, life-year; QALY, quality-adjusted life-year; SC, standard care; SSR, SSR cost; USD, US dollar; WAC, wholesale acquisition cost.

^a Lifetime analysis was based on microsimulation and probabilistic sensitivity analysis used population means for parameters involved.

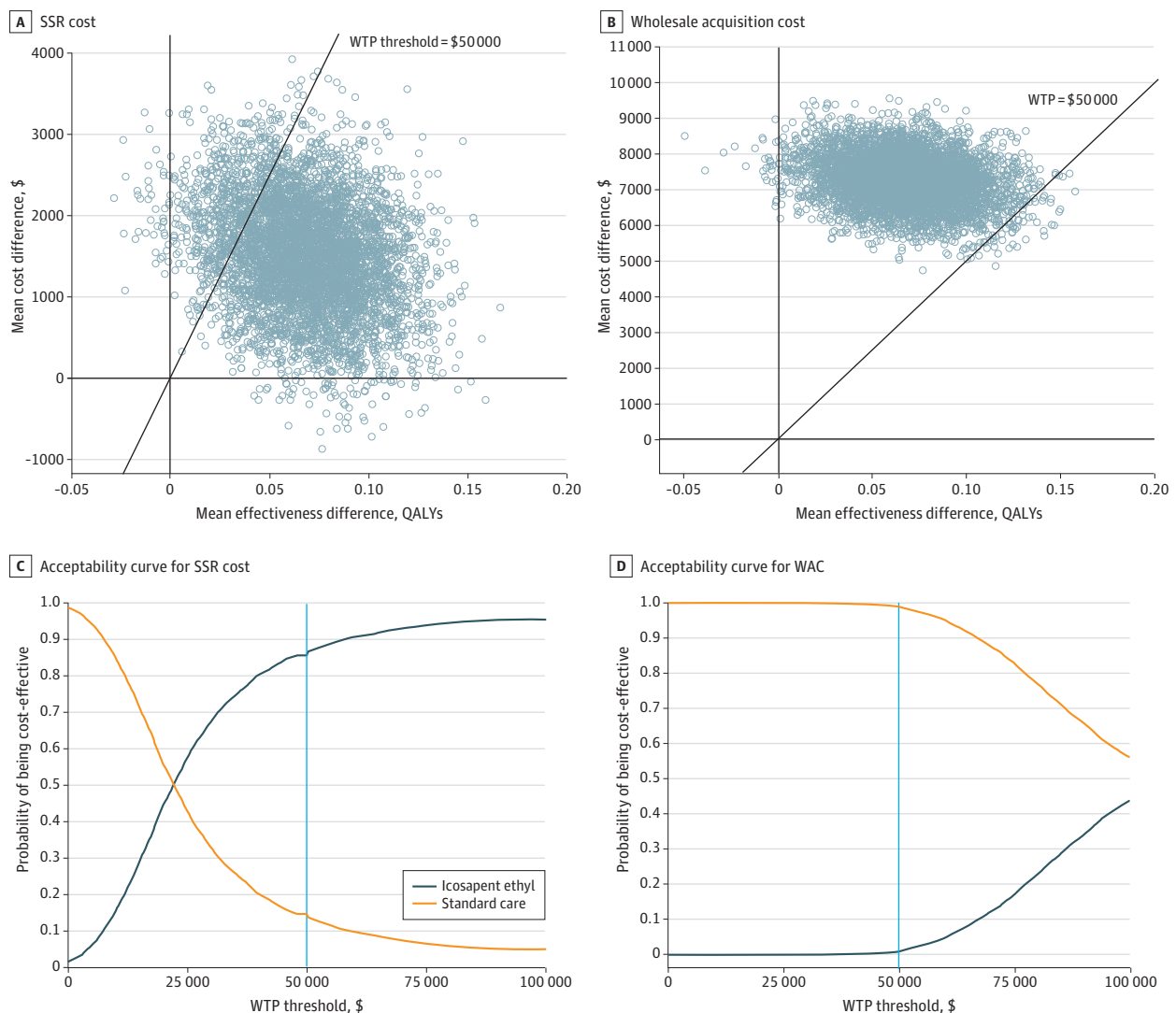
Subgroup Analysis

For most subgroups, the ICERs indicate that IPE is dominant or cost-effective below a WTP threshold of \$100 000 per QALY gained using SSR costs or WAC in-trial (eTable 11 in the Supplement) and over the lifetime (eTable 12 in the Supplement).

Discussion

In-trial, IPE was estimated to cost \$22 311 per QALY gained using the SSR cost and \$107 218 per QALY gained using the WAC. In lifetime extrapolation, IPE was projected to cost less and be more effective than standard care using SSR cost, but not using WAC (ICER, \$23 866 per QALY gained). In the probabilistic sensitivity analysis, the ICER was less than \$50 000 per QALY gained in 86.2% of simulations using SSR cost and 67.2% of simulations using WAC. Although lifetime analysis remains a standard for cost-effectiveness analysis,¹⁰ the in-trial analysis, with a 4.9-year median follow-up, uses real observed data, without the modeling and assumptions necessary for a lifetime analysis. We

Figure 1. Cost-effectiveness Planes During the Trial Period Using National Inpatient Sample Costs for Events



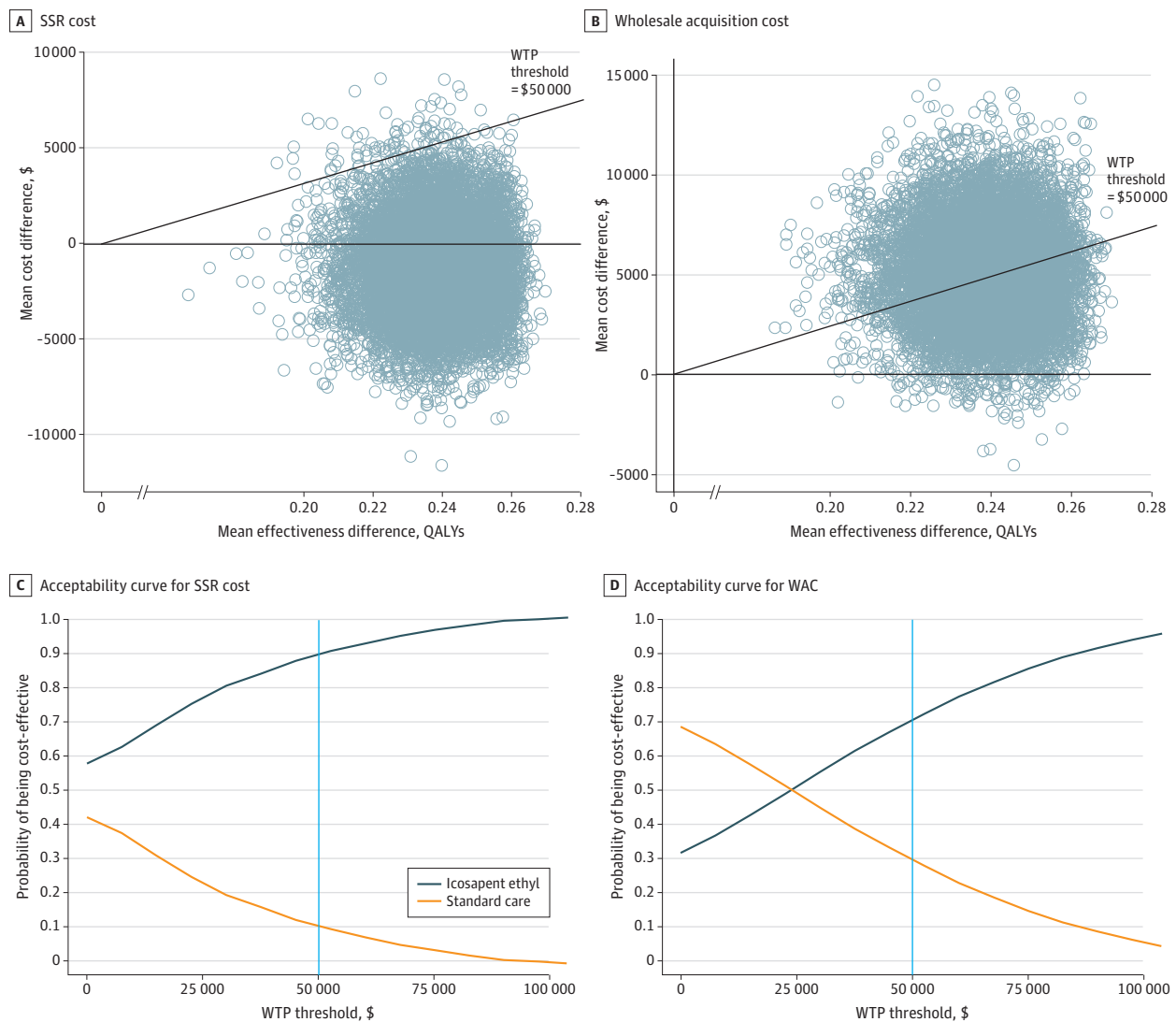
A, Cost-effectiveness plane for SSR cost. B, Cost-effectiveness plane for wholesale acquisition cost (WAC). C, Acceptability curve for SSR cost. D, Acceptability curve for WAC. QALY indicates quality-adjusted life-year; and WTP, willingness-to-pay.

completed a broad range of analyses investigating posttrial treatment effect, medication and outcome pricing, adherence, and subgroups. The ICER is highly sensitive to the cost of IPE. The SSR cost and WAC offer reasonable boundaries of real-world costs of IPE, as shown in Figure 3.

Comparison With Other Treatments

The cost-effectiveness of IPE, based on SSR cost, is consistent with the cost-effectiveness of statins, which, as generic formulations, are cost saving for secondary prevention. In contrast, proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors have lower value, given their high annual cost even after discounts.³³⁻³⁵ In the study by Kazi et al,³³ the annual cost of the PCSK9 inhibitor alirocumab was \$7187 (range, \$2640-\$18 200) based on pricing from SSR Health (net cost)¹⁶ and RedBook (WAC).³⁶ The ICER for alirocumab plus a statin was \$308 000 (range, \$197 000-\$678 000). In the same publication, the ICER for ezetimibe (at an annual cost of \$1411) plus a statin was \$81 000 (range, \$51 000-\$215 000). In the present analysis, the cost-effectiveness of IPE was sensitive to the price of the drug.

Figure 2. Cost-effectiveness Planes Over the Lifetime Using National Inpatient Sample Costs for Events



A, Cost-effectiveness plane for SSR cost. B, Cost-effectiveness plane for wholesale acquisition cost (WAC). C, Acceptability curve for SSR cost. D, Acceptability curve for WAC. QALY indicates quality-adjusted life-year; and WTP, willingness-to-pay.

Comparison With Other Studies of Icosapent Ethyl

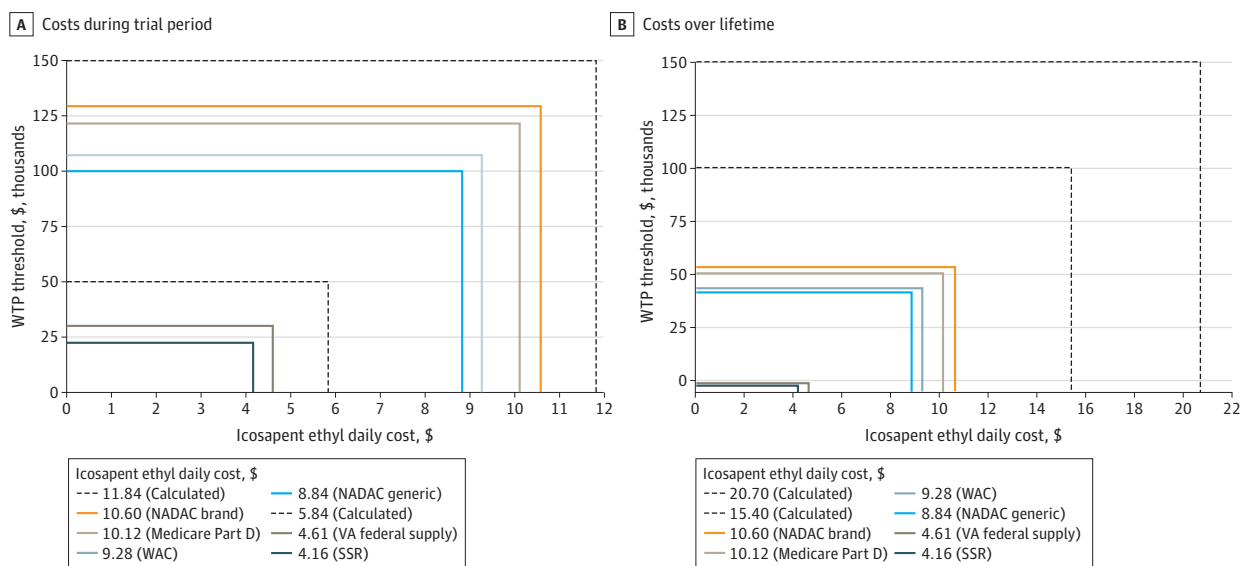
The Institute for Clinical and Economic Review group used a Markov model simulation based on published summary results from REDUCE-IT³⁷ and found that the ICER for IPE at a net price of \$4.44 per day compared with standard care was \$17 000 per QALY gained.³⁸ These results are in accord with the present analysis showing that IPE is cost-effective for high-risk populations; although the cost of the drug was similar to the SSR cost in this study, there are differences that likely account for the results. The Institute for Clinical and Economic Review group used published summary data, and the present analysis used patient-level data from the REDUCE-IT trial database, affording a more granular, detailed analysis and making it easier to include and cost all events and reducing the number of assumptions applied in the model. For instance, evaluating the incidence of coronary artery bypass grafting surgery and percutaneous coronary intervention required direct access to patient-level data, and the published summary data did not include repeated events. In addition, the cost of events in the Institute for Clinical and Economic Review group study was drawn from multiple sources across many years; some were state specific and some national, and they date as far back as 2003.

Gao et al³⁹ used a Markov model simulation to evaluate the cost-effectiveness of IPE from an Australian health care perspective, finding an ICER of A\$59 036 (approximately \$42 151 USD) per QALY gained. That study considered only first events, the costs for events were lower than in the present study, and it is not clear what costs were used for revascularization.

Strengths and Limitations

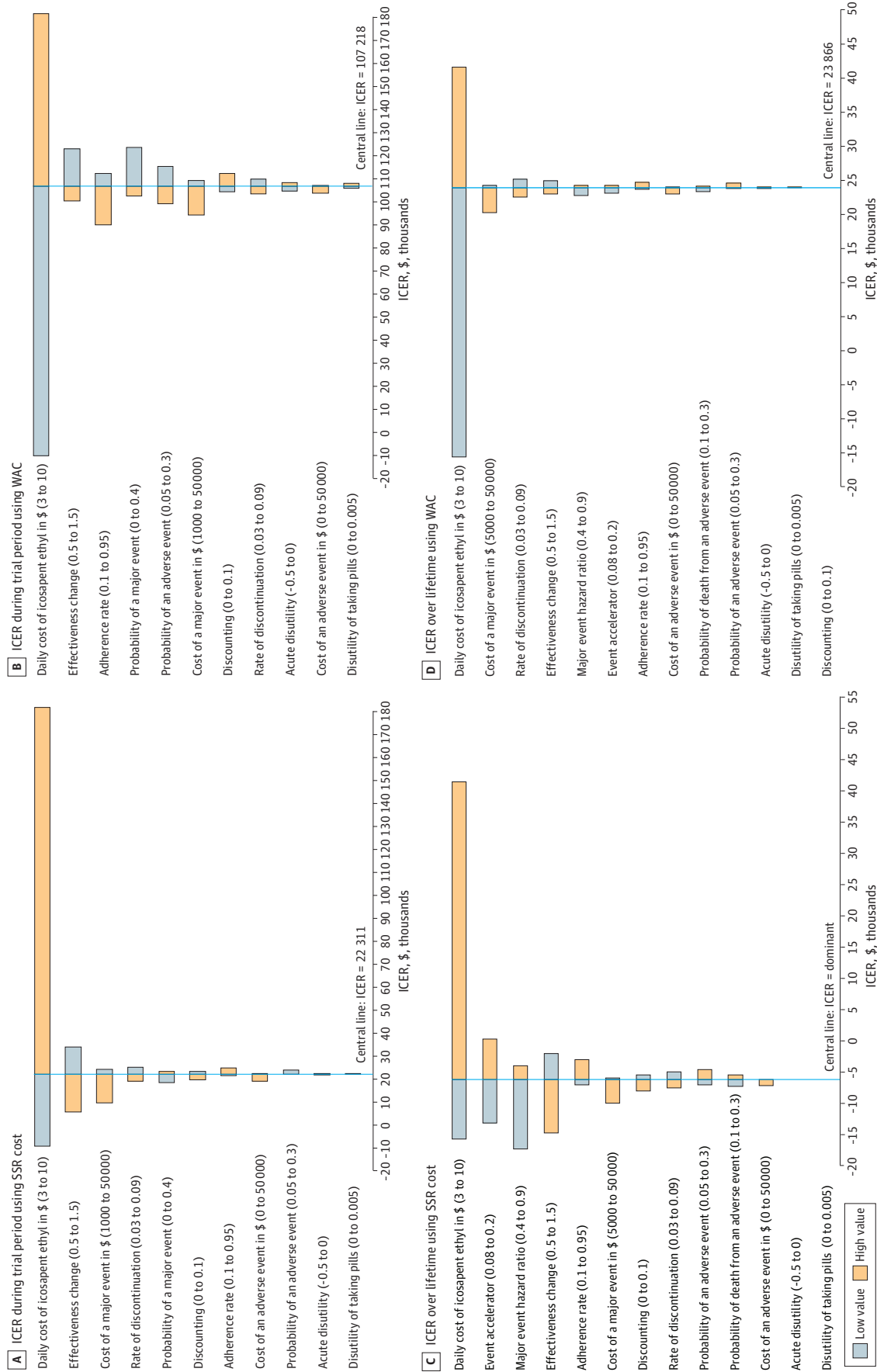
This study has some strengths, including that this was a patient-level analysis during the trial period, including all CVD events. In addition to the main end points, additional cardiovascular events and serious adverse events were considered when rates differed between the study groups. Hospital charges reduced to costs by the cost to charge ratio from the National Inpatient Sample with the addition of physician costs were used as a proxy for societal costs.^{12,14} To carefully construct a cost model that accurately reflects costs, National Inpatient Sample costing was used for events and both SSR cost and WAC for IPE.¹⁶ The SSR cost accounts for the lower prices actually paid for the drug compared with WAC. The SSR Health pricing model is appropriate for branded drugs, especially if they are still protected by a patent. The incremental effectiveness and cost were sensitive to the cost

Figure 3. Icosapent Ethyl Daily Costs for Various Willingness-to-Pay (WTP) Thresholds



A, Costs during the trial period. B, Costs over the lifetime. NADAC indicates National Average Drug Acquisition Cost; VA, Veterans Administration; and WAC, wholesale acquisition cost.

Figure 4. Tornado Diagrams for Incremental Cost-effectiveness Ratio (ICER)



A, ICER during the trial period using SSR Health net cost (SSR cost). B, ICER during the trial period using wholesale acquisition cost (WAC). C, ICER over the lifetime using SSR cost. D, ICER over the lifetime using WAC. Gray bar indicates low value, and orange bar indicates high value, separated by central line (ICER).

of the drug as well as events. Otherwise, sensitivity and scenario analyses found little association with the ICER, confirming the robustness of these results.

This study also has some limitations, including that utility was not measured during REDUCE-IT, so published sources were used as a proxy. The lifetime analysis required modeling to estimate survival, event rates, adherence, and costs; there is considerable uncertainty to these values beyond the trial period, although the model performed well compared with the 4.9-year follow-up available (eTable 9 and eFigure 3 in the Supplement), and despite these assumptions, the ICER remained in an acceptable range in a series of sensitivity analyses. Some direct care costs likely to favor IPE, such as rehabilitation or skilled nursing facilities, were not captured in our costing models. We also did not include indirect costs, such as lost employment, travel, or caregiver costs, which would also favor IPE. Although we strive to model costs and benefits for a health care sector perspective, proxies must be used for cost, and there is no perfect source. Also, the costs used in the present study are from the US health care system and cannot be directly applied to other countries. Costs were established for all patients as if all patients had received care in the US. This model assumes similar resource use for US and non-US patients. No geographical interactions were noted in the clinical results of REDUCE-IT.⁸

Conclusions

In this patient-level cost-effectiveness analysis of REDUCE-IT, IPE was projected to be cost-effective compared with standard care, both during the trial and over a lifetime, with an ICER below commonly accepted WTP thresholds. The findings suggest that treatment with IPE may be cost-effective among patients with high cardiovascular risk whose triglyceride levels remain high despite statin therapy.

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REFERENCES

1. Fruchart JC, Sacks F, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol*. 2008;102(10 suppl):1K-34K. doi:10.1016/S0002-9149(08)01833-X
2. Bhatt DL, Miller M, Brinton EA, et al; REDUCE-IT Investigators. REDUCE-IT USA: results From the 3146 patients randomized in the United States. *Circulation*. 2020;141(5):367-375. doi:10.1161/CIRCULATIONAHA.119.044440
3. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. *J Am Coll Cardiol*. 2019;73(22):2791-2802. doi:10.1016/j.jacc.2019.02.032
4. Granger CB, Nelson AJ, Pagidipati NJ. Risk of total events with icosapent ethyl: can we reduce it? *J Am Coll Cardiol*. 2019;73(22):2803-2805. doi:10.1016/j.jacc.2019.03.492
5. Peterson BE, Bhatt DL, Steg PG, et al. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT revascularization analyses. *Circulation*. 2021;143(1):33-44. doi:10.1161/CIRCULATIONAHA.120.050276
6. Gaba P, Bhatt DL, Giugliano RP, et al. Comparative reductions in investigator-reported and adjudicated ischemic events in REDUCE-IT. *J Am Coll Cardiol*. 2021;78(15):1525-1537. doi:10.1016/j.jacc.2021.08.009
7. Bhatt DL, Steg PG, Brinton EA, et al; REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. *Clin Cardiol*. 2017;40(3):138-148. doi:10.1002/clc.22692
8. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792
9. Huserau D, Drummond M, Petrou S, et al; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013;346:f1049. doi:10.1136/bmj.f1049
10. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195
11. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40(4):381-387. doi:10.1038/sj.bmt.1705727
12. Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Overview of the National (Nationwide) Inpatient Sample (NIS). Accessed May 14, 2020. <https://www.hcup-us.ahrq.gov/nisoverview.jsp>
13. Bress AP, Bellows BK, King JB, et al; SPRINT Research Group. Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;377(8):745-755. doi:10.1056/NEJMsa1616035
14. Peterson C, Xu L, Florence C, Grosse SD, Annet JL. Professional fee ratios for US hospital discharge data. *Med Care*. 2015;53(10):840-849. doi:10.1097/MLR.0000000000000410
15. Centers for Medicare & Medicaid Services. Health expenditures by age and gender. Accessed July 15, 2020. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Age-and-Gender>
16. SSR Health. Home page. Accessed July 15, 2020. <https://www.ssrhealth.com/>
17. Dunn A, Grosse SD, Zuvekas SH. Adjusting health expenditures for inflation: a review of measures for health services research in the United States. *Health Serv Res*. 2018;53(1):175-196. doi:10.1111/1475-6773.12612
18. Arias E, Xu J. United States life tables, 2017. *Natl Vital Stat Rep*. 2019;68(7):1-66.
19. Cohen DJ, Osnabrugge RL, Magnuson EA, et al; SYNTAX Trial Investigators. Cost-effectiveness of percutaneous coronary intervention with drug-eluting stents versus bypass surgery for patients with 3-vessel or left main coronary artery disease: final results from the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2014;130(14):1146-1157. doi:10.1161/CIRCULATIONAHA.114.009985
20. Gidwani R, Russell LB. Estimating transition probabilities from published evidence: a tutorial for decision modelers. *Pharmacoeconomics*. 2020;38(11):1153-1164. doi:10.1007/s40273-020-00937-z
21. Moran AE, Forouzanfar MH, Roth GA, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation*. 2014;129(14):1483-1492. doi:10.1161/CIRCULATIONAHA.113.004042
22. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223. doi:10.1016/S0140-6736(12)61689-4

23. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. *JAMA*. 2016;316(7):743-753. doi:10.1001/jama.2016.11004
24. Hutchins R, Viera AJ, Sheridan SL, Pignone MP. Quantifying the utility of taking pills for cardiovascular prevention. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):155-163. doi:10.1161/CIRCOUTCOMES.114.001240
25. Hutchins R, Pignone MP, Sheridan SL, Viera AJ. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. *BMJ Open*. 2015;5(5):e006505. doi:10.1136/bmjopen-2014-006505
26. Mahoney EM, Chu H. Cost-effectiveness analysis alongside clinical trials: statistical and methodological issues. In: Weintraub WS, ed. *Cardiovascular Health Care Economics*. Humana Press; 2003:123-156. doi:10.1385/1-59259-398-4:123
27. Zhang Z, Kolm P, Grau-Sepulveda MV, et al. Cost-effectiveness of revascularization strategies: the ASCERT study. *J Am Coll Cardiol*. 2015;65(1):1-11. doi:10.1016/j.jacc.2014.09.078
28. Anderson JL, Heidenreich PA, Barnett PG, et al; ACC/AHA Task Force on Performance Measures; ACC/AHA Task Force on Practice Guidelines. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129(22):2329-2345. doi:10.1161/CIR.0000000000000042
29. Baio G, Dawid AP. Probabilistic sensitivity analysis in health economics. *Stat Methods Med Res*. 2015;24(6):615-634. doi:10.1177/0962280211419832
30. Henk HJ, Paoli CJ, Gandra SR. A Retrospective study to examine healthcare costs related to cardiovascular events in individuals with hyperlipidemia. *Adv Ther*. 2015;32(11):1104-1116. doi:10.1007/s12325-015-0264-7
31. Case BC, Bress AP, Kolm P, et al. The economic burden of hypertriglyceridemia among US adults with diabetes or atherosclerotic cardiovascular disease on statin therapy. *J Clin Lipidol*. 2019;13(5):754-761. doi:10.1016/j.jacl.2019.07.004
32. Moazzami K, Dolmatova E, Maher J, et al. In-hospital outcomes and complications of coronary artery bypass grafting in the United States between 2008 and 2012. *J Cardiothorac Vasc Anesth*. 2017;31(1):19-25. doi:10.1053/j.jvca.2016.08.008
33. Kazi DS, Penko J, Coxson PG, Guzman D, Wei PC, Bibbins-Domingo K. Cost-effectiveness of alirocumab: a just-in-time analysis based on the ODYSSEY Outcomes Trial. *Ann Intern Med*. 2019;170(4):221-229. doi:10.7326/M18-1776
34. Bhatt DL, Briggs AH, Reed SD, et al; ODYSSEY OUTCOMES Investigators. Cost-effectiveness of alirocumab in patients with acute coronary syndromes: the ODYSSEY OUTCOMES Trial. *J Am Coll Cardiol*. 2020;75(18):2297-2308. doi:10.1016/j.jacc.2020.03.029
35. Weintraub WS, Boden WE. PCSK9 inhibition for therapeutic decision-making: assessing the value. *J Am Coll Cardiol*. 2020;75(18):2309-2311. doi:10.1016/j.jacc.2020.03.037
36. IBM. IBM Micromedex RED BOOK. Accessed July 15, 2020. <https://www.ibm.com/products/micromedex-red-book>
37. Institute for Clinical and Economic Review. Cardiovascular disease: additive therapies. Accessed July 15, 2020. <https://icer.org/assessment/cvd-additive-therapies-2019/>
38. Mensah GA, Cooper RS, Siega-Riz AM, et al. Reducing cardiovascular disparities through community-engaged implementation research: a National Heart, Lung, and Blood Institute workshop report. *Circ Res*. 2018;122(2):213-230. doi:10.1161/CIRCRESAHA.117.312243
39. Gao L, Moodie M, Li SC. The cost-effectiveness of omega-3 polyunsaturated fatty acids—the Australian healthcare perspective. *Eur J Intern Med*. 2019;67:70-76. doi:10.1016/j.ejim.2019.07.001

SUPPLEMENT.

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