

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

The potential population health impact of treating REDUCE-IT eligible US adults with Icosapent Ethyl

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ARTICLE INFO

Keywords:

Cardiovascular disease
Antihypercholesteremic agents
Hypertriglyceridemia
Costs and cost analysis

ABSTRACT

Objective: To explore the population health impact of treating all US adults eligible for the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) with icosapent ethyl (IPE), we estimated (1) the number of ASCVD events and healthcare costs that could be prevented; and (2) medication costs. **Methods:** We derived REDUCE-IT eligible cohorts in (1) the National Health and Nutrition Examination Surveys (NHANES) 2009-2014 and (2) the Optum Research Database (ORD). Population sizes were obtained from NHANES and observed first event rates (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, or coronary revascularization) were estimated from the ORD. Hazard ratios from REDUCE-IT USA estimated events prevented with IPE therapy. The National Inpatient Sample estimated event costs (facility and professional) and daily IPE treatment cost was approximated at \$4.59.

Results: We estimate 3.6 million US adults to be REDUCE-IT eligible, and the observed five-year first event rate without IPE of 19.0% (95% confidence interval [CI] 16.6%-19.5%) could be lowered to 13.1% (95% CI 12.8%-13.5%) with five years of IPE treatment, preventing 212,000 (uncertainty range 163,000-262,000) events. We projected the annual IPE treatment cost for all eligible persons to be \$6.0 billion (95% CI \$4.7-\$7.5 billion), but saving \$1.8 billion annually due to first events prevented (net annual cost \$4.3 billion). The total five-year event rate (first and recurrent) could be reduced from 42.5% (95% CI 39.6%-45.4%) to 28.9% (95% CI 26.9-30.9%) with five years of IPE therapy, preventing 490,000 (uncertainty range 370,000-609,000) events (net annual cost \$2.6 billion).

Conclusions: Treating all REDUCE-IT eligible US adults has substantial medication costs but could prevent a substantial number of ASCVD events and associated direct costs. Indirect cost savings by preventing events could outweigh much of the incurred direct costs.

The American Heart Association (AHA)/American College of Cardiology (ACC) cholesterol guidelines emphasize that the cornerstone of

treatment for dyslipidemias is statin therapy added to healthy lifestyle interventions [1]. However, despite statin treatment, 12.3 million

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, Atherosclerotic cardiovascular disease; CI, Confidence interval; HDL, High-density lipoprotein cholesterol; IPE, icosapent ethyl; IQR, Interquartile range; LDL-C, Low-density lipoprotein cholesterol; M, Million; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Surveys; NNT, Number needed to treat; ORD, Optum Research Database; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TG, Triglyceride; UR, Uncertainty range; US, United States.

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<https://doi.org/10.1016/j.ajpc.2022.100345>

Received 27 January 2022; Received in revised form 18 April 2022; Accepted 25 April 2022

Available online 28 April 2022

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United States (US) adults have residual hypertriglyceridemia (triglycerides [TG] ≥ 150 mg/dL) [2,3]. Hypertriglyceridemia is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) events, mechanistically by elevating small very low density lipoproteins, intermediate density lipoproteins, and chylomicron remnants [4,5]. The international Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) showed that icosapent ethyl (IPE) 4 g/day when added to contemporary medical care including statin treatment reduced the risk of time to the first event of the primary composite outcome (cardiovascular death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization, or unstable angina) by 25% (31% in the higher-risk, US subgroup), and reduced the risk of total (first and recurrent) events by 32% [6–8]. Further, IPE added to statin therapy is cost-effective compared with usual care in the US and Germany [9,10].

We sought to: 1) characterize the US adult population who meet the enrollment criteria for REDUCE-IT; 2) calculate the number of ASCVD events that would be expected with and without IPE treatment among REDUCE-IT eligible US adults; 3) estimate the annual cost to treat all REDUCE-IT eligible US adults with IPE; and 4) estimate the overall economic impact of IPE therapy considering the offset of drug costs by events prevented.

1. Methods

We developed two REDUCE-IT eligible cohorts: one using the National Health and Nutrition Examination Surveys (NHANES), and another using the Optum Research Database (ORD). To estimate the population health impact of IPE treatment, we constructed three inputs described in detail below: 1) Population sizes of US adults meeting REDUCE-IT eligibility criteria; 2) Five-year and annual ASCVD event rates among REDUCE-IT eligible US adults with and without IPE treatment; and 3) Annual IPE medication costs and cost of ASCVD events prevented by treating all REDUCE-IT eligible adults with IPE. The University of Utah Institutional Review Board determined this study to be exempt.

In REDUCE-IT, [6,7,11–15] participants were eligible for enrollment if they were 50 years of age and had diabetes and at least one additional risk factor (primary prevention group) or 45 years of age or older and had pre-existing ASCVD (secondary prevention group). Participants had to have a fasting TG level of 135–499 mg/dL and low-density lipoprotein cholesterol (LDL-C) level of 41–100 mg/dL while taking a stable dose of a statin for at least four weeks. Key exclusion criteria included current pregnancy or severe heart failure, liver disease, or renal disease. Of the 8,179 participants enrolled and randomized, 3,146 were in the US (38.5%), and baseline characteristics were similar between REDUCE-IT and REDUCE-IT USA participants [8]. We developed an abridged set of eligibility criteria using data available in both NHANES and ORD to identify REDUCE-IT eligible cohorts (Supplemental Table S1).

Nationally-representative population sizes were estimated by applying REDUCE-IT eligibility criteria to NHANES, which can be used to produce estimates for the non-institutionalized civilian US adult population (see Supplemental Methods for information about NHANES) [16,17]. To create an NHANES cohort contemporary to the ORD cohort (which allowed for five-year follow-up through December 31, 2019), we pooled participants of three consecutive two-year cycles (2009–2010, 2011–2012, and 2013–2014) to provide more stable estimates [18]. Of 30,468 participants, 124 met the abridged eligibility criteria and were included in the current analysis (Supplemental Figure S1). Definitions for each variable are described in the Supplemental Methods and Supplemental Table S2 [19,20].

We studied the primary composite outcome in REDUCE-IT: cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. We also analyzed each component of the composite separately.

We used the ORD to estimate observed event rates (i.e., the event

rates that would be expected without IPE treatment). The ORD includes de-identified medical and pharmacy claims data, including linked insurance enrollment, for commercial and Medicare Advantage enrollees, representing over 70 million lives in the US. In 2018, approximately 19% of the US commercially enrolled population and 21% of the Medicare Advantage population were represented in the ORD. The index date was the date of the first non-missing TG value in the range of 135–499 mg/dL in the identification period of January 1, 2009, and December 31, 2014. This date range was selected to allow for a minimum follow-up of five years, similar to the median follow-up time in REDUCE-IT of 4.9 years. Of 1,202,141 ORD members with an eligible TG value in the index identification period, 47,422 were included in the present analysis who met the abridged REDUCE-IT eligibility criteria and were eligible for data linkage to the National Death Index to ascertain fatal outcomes (Supplemental Figure S2).

Definitions for baseline characteristics are provided in Supplemental Table S2. Each eligible ORD member was followed for up to five years to identify the first occurrence of the composite outcome and its individual components. Censoring occurred at the first of: an ASCVD event; death; five years; December 31, 2019; or loss or disenrollment from the health plan.

The hazard ratios from the REDUCE-IT USA analysis [8] were used to estimate the annual and five-year event rates with IPE treatment (see Supplemental Methods). For an analysis of total events (i.e., first and recurrent events) expected without IPE treatment, total (first plus recurrent) event rates from the REDUCE-IT USA analysis were used (Supplemental Figure 6 from the Bhatt et al manuscript [8]).

The SSR Health cost of \$4.59/day was selected to estimate IPE treatment cost because it provides a realistic estimate of the medication cost to the consumer after discounts and rebates. Event costs (facility and professional) were estimated from the National Inpatient Sample according to the published REDUCE-IT cost-effectiveness analysis [9]. All costs were inflated to 2021 US Dollars using the annual medical care component of the Consumer Price Index [21]. For event costs associated with the composite outcome, a weighted mean cost per event was calculated based on the observed event rates. For disease burden estimates, using the ORD, we approximated an average cost of outpatient medical care per REDUCE-IT eligible person annually without IPE treatment [22]. Indirect costs are typically not assessed in budget impact analyses such as ours. However, using a technical report published for the AHA, [23] we project an annual indirect cost burden per person with coronary heart disease (see Supplemental Methods), which we then projected to the REDUCE-IT eligible NHANES population size.

We calculated characteristics of REDUCE-IT eligible NHANES participants and ORD members overall. The NHANES sampling weights and the complex sampling design were applied in all calculations to obtain nationally representative prevalence estimates. The 95% confidence intervals (CIs) of each NHANES REDUCE-IT eligible group were calculated using Taylor-series variance estimation [24]. For simplicity, the NHANES population sizes for further calculations were rounded to the nearest 100,000.

The observed five-year ASCVD event rates in the REDUCE-IT eligible ORD members were multiplied by the NHANES population sizes to estimate the number of events expected without IPE treatment over a five-year period. Because the Kaplan-Meier method overestimates the cumulative incidence in the presence of a competing risk event, we calculated five-year ASCVD event rates while accounting for the competing risk of all-cause mortality [25]. Then, we multiplied the expected number of ASCVD events without IPE treatment by the hazard ratios in REDUCE-IT USA [8] (Supplemental Table S3) to project the expected number of events and number of events prevented with IPE treatment over a five-year period. Annual event rates were derived from the five-year rates by assuming a constant hazard across time (Supplemental Methods). The SSR Health cost of IPE was multiplied by the NHANES population sizes to approximate the annual cost of treating all REDUCE-IT eligible patients. Then, mean event costs were multiplied by

the annual number of events that would be expected to be prevented with IPE, summing to a total cost of events prevented with one year of IPE treatment. We projected the average outpatient medical costs in the REDUCE-IT eligible population annually by multiplying the NHANES population sizes by the average outpatient medical burden per year estimated in ORD. We estimated the annual indirect costs in the REDUCE-IT eligible population by multiplying the estimated indirect costs per person by the NHANES population sizes. We further calculated treatment efficiency, defined as the number of ASCVD events prevented per 1000 eligible individuals treated with IPE for 5 years, and a five-year number-needed-to treat (NNT). We calculated standard errors for our estimates of population size and incremental costs associated using the CIs of these estimates assuming a normal distribution. We used the estimated means and standard errors of population size and incremental cost to calculate confidence intervals for our estimate of annual cost burden. To quantify uncertainty, an analysis-of-extremes was conducted in which the number of ASCVD events prevented was recalculated using the upper and lower 95% CI bounds of both the hazard ratio from REDUCE-IT USA and observed event rates. For population health benefit, the uncertainty ranges (UR) represent the lower and upper bounds from the analysis-of-extremes approach.

Secondarily, we evaluated the total number of ASCVD events annually (first and recurrent) expected with and without IPE treatment. Analyses were repeated among subgroups of cardiovascular prevention group, ezetimibe use, baseline diabetes, baseline eGFR, and baseline TG. Because cost-effectiveness estimates appear to be sensitive to the price of IPE, [9] we conducted two sensitivity analyses on cost estimates: 1) reducing the SSR Health cost by 20% to account for the 6% reduction in adherence observed throughout the REDUCE-IT trial [6]; and 2) using the RED BOOK wholesale acquisition cost of \$11.48/day.

Analyses were completed using SAS v.9.4 (SAS Institute, Cary, NC).

2. Results

Characteristics of the REDUCE-IT eligible NHANES and ORD cohorts compared to the REDUCE-IT USA participants are shown in Table 1. The REDUCE-IT-eligible NHANES and ORD cohorts were older (median 67.7 and 68.0 years) compared with REDUCE-IT USA (65.0 years). The REDUCE-IT USA cohort had a smaller proportion of participants compared to the REDUCE-IT-eligible NHANES and ORD cohorts who were Black (3.9% vs. 4.4% and 10.1%), did not have diabetes (29.9% vs. 36.2% and 32.7%), and had TG <150 mg/dL (10.6% vs. 23.2% and 27.9%) or 150-199 mg/dL (28.1% vs. 43.9% and 44.6%). Among REDUCE-IT USA, NHANES, and ORD, 41.2%, 47.1%, and 35.9% met criteria for primary prevention, respectively. On the median, REDUCE-IT USA participants had a higher TG, lower HDL-C, and lower LDL-C than REDUCE-IT-eligible NHANES and ORD participants.

Overall, 3.6 million US adults met the REDUCE-IT enrollment criteria (Table 2; 95% CI 2.8-4.5 million). Of these, 1.7 million (95% CI 1.3-2.1 million) and 1.9 million (95% CI 1.2-2.7 million) met criteria for primary and secondary prevention, respectively.

Overall, the observed five-year ASCVD event rate among REDUCE-IT eligible ORD members was 19.0% (95% CI 18.6%-19.5%), which approximates 684,000 first (not total) events (95% CI 523,000-845,000) nationally over five years without IPE treatment (Table 2). If all REDUCE-IT eligible US adults were treated with IPE for five years added to usual care, the event rate is estimated to be 13.1% (95% CI 12.8%-13.5%), or about 472,000 first events (95% CI 360,000-583,000). Over five years, with IPE treatment added to usual care, 212,000 first events could be prevented (UR 163,000-262,000), and 5.9 events could be prevented per 1,000 eligible US adults (UR 5.8-6.0). The number of persons needed to be treated for five years to prevent one event (i.e., the five-year NNT) could be 16.9 (UR 16.7-17.2). With five years of IPE treatment, the number of total events (first and recurrent) could be reduced by 490,000 (UR 370,000-609,000), or 13.6 events per 1000 eligible US adults (UR 12.7-14.5), and the five-year NNT could be 7.4

Table 1

Characteristics of the REDUCE-IT USA, NHANES 2009-2014 REDUCE-IT eligible, and Optum Research Database REDUCE-IT eligible populations.

Characteristic	REDUCE-IT USA (n=3,146)	NHANES REDUCE-IT eligible (n=124, weighted N=3,636,264)	Optum Research Database REDUCE-IT eligible (n=47,422)
Age			
Median (IQR), years	65.0 (59.0-71.0)	67.7 (61.4-74.6)	68.0 (60.0-75.0)
≥65 years	1674 (53.2%)	81 (2.2M, 60.7%)	28,791 (60.7%)
Male	2131 (67.7%)	72 (2.1M, 58.6%)	25,661 (54.1%)
Race-ethnicity*			
White	2911 (92.5%)	83 (3.1M, 86.2%)	33,600 (70.9%)
Black	124 (3.9%)	14 (0.1M, 4.4%)	4,777 (10.1%)
Hispanic	306 (9.7%)	20 (0.2M, 4.7%)	4,251 (9.0%)
Asian	69 (2.2%)	N/A**	1,673 (3.5%)
Other/Multiple	42 (1.3%)	7 (0.2M, 4.7%)	3,121 (6.6%) [†]
Cardiovascular risk stratum			
Primary prevention	1296 (41.2%)	56 (1.7M, 47.1%)	17,045 (35.9%)
Secondary Prevention	1850 (58.8%)	68 (1.9M, 52.9%)	30,377 (64.1%)
Ezetimibe use			
Diabetes	202 (6.4%)	5 (0.1M, 2.6%)	2,950 (6.2%)
Present	2205 (70.1%)	82 (2.3M, 63.8%)	31,896 (67.3%)
Absent	941 (29.9%)	42 (1.3M, 36.2%)	15,526 (32.7%)
TG, mg/dL			
Median (IQR)	217.0 (175.0-273.5)	177.6 (150.5-239.3)	168.0 (148.0-205.0)
<150	333 (10.6%)	27 (0.8M, 23.2%)	13,237 (27.9%)
150-199	885 (28.1%)	54 (1.6M, 43.9%)	21,167 (44.6%)
≥200	1924 (61.2%)	43 (1.2M, 32.9%)	13,018 (27.5%)
HDL-C, mg/dL, median (IQR)	39.5 (34.0-46.5)	42.0 (33.6-49.5)	43.0 (36.0-51.0)
LDL-C, mg/dL, median (IQR)	72.0 (60.0-85.0)	77.4 (60.3-91.5)	76.0 (64.0-88.0)

* REDUCE-IT USA proportions may total greater than 100% due to non-mutually exclusive reporting of race and ethnicity in the REDUCE IT USA subgroup analysis.

** Estimate could not be calculated because Asian race was not available in the 2009-2010 survey cycle

[†] Includes 2,759 members (5.38%) with missing, unknown, or no socioeconomic status data.

HDL: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; M: million; NHANES: National Health and Nutrition Examination Survey; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TG: triglyceride

Numbers in table are represented as number (percentage) or median (interquartile range), unless otherwise stated.

(UR 6.9-7.9). In subgroups, the five-year NNT was projected to be lowest among patients with an eGFR <60 mL/min/1.73m², (8.9, UR 8.6-9.3; Supplemental Table S5) and highest among primary prevention patients (60.8, UR 57.2-64.7).

To treat all 3.6 million REDUCE-IT eligible US adults with IPE for one year is projected to cost \$6.0 billion (UR \$4.7-\$7.5 billion; Table 3). Using a WAC estimate of \$11.48/day, the annual IPE treatment cost would be \$15.1 billion (UR \$11.7-18.9 billion). Discounting the SSR Health cost by 20% to account for nonadherence to a daily cost of \$3.67/day would result in a projected annual treatment cost of \$4.8 billion (UR \$3.8-6.0 billion). Assuming a weighted mean cost of \$32,980 (95% CI \$20,619-\$45,341) per event and, by preventing 50,000 first ASCVD events with one year of IPE treatment, \$1.8 billion in event costs

Table 2

Observed and predicted 5-year event rates of the REDUCE-IT primary and secondary outcomes if REDUCE-IT eligible US adults were treated with icosapent ethyl, accounting for competing risk of all-cause death.

Outcome	REDUCE-IT eligible US adults in millions, NHANES (95% CI)	Observed 5-year composite* event rates		Predicted 5-year ASCVD event rates if treated with icosapent ethyl		ASCVD events prevented with icosapent ethyl use, thousands (UR)	ASCVD events prevented per 1000 eligible individuals treated with icosapent ethyl (UR)	Number needed to treat for 5 years (UR)
		% (95% CI)	Total number per 5-years, thousands (95% CI)	% (95% CI)	Total number per 5-years, thousands (95% CI)			
Primary composite outcome*								
First events only	3.6 (2.8-4.5)	19.0 (18.6-19.5)	684 (523-845)	13.1 (12.8-13.5)	472 (360-583)	212 (163-262)	5.9 (5.8-6.0)	16.9 (16.7-17.2)
Total events**	3.6 (2.8-4.5)	42.5 (39.6-45.4)	1,530 (1,156-1,904)	28.9 (26.9-30.9)	1,040 (786-1,294)	490 (370-609)	13.6 (12.7-14.5)	7.4 (6.9-7.9)
Cardiovascular death	3.6 (2.8-4.5)	4.4 (4.2-4.7)	158 (120-197)	2.9 (2.8-3.1)	104 (79-129)	54 (41-67)	1.5 (1.4-1.6)	66.7 (62.5-71.4)
Nonfatal myocardial infarction	3.6 (2.8-4.5)	5.7 (5.4-6.0)	205 (156-254)	4.1 (3.9-4.3)	148 (112-183)	58 (44-72)	1.6 (1.5-1.7)	62.5 (58.8-66.7)
Nonfatal stroke	3.6 (2.8-4.5)	5.5 (5.3-5.8)	198 (151-245)	3.5 (3.3-3.7)	126 (96-156)	72 (55-89)	2.0 (2.0-2.1)	50.0 (47.6-50.0)
Coronary revascularization	3.6 (2.8-4.5)	7.6 (7.3-7.9)	274 (209-339)	4.9 (4.7-5.1)	176 (134-218)	97 (74-120)	2.7 (2.6-2.8)	37.0 (35.7-38.5)
Unstable angina	3.6 (2.8-4.5)	2.7 (2.5-2.9)	97 (73-121)	1.4 (1.3-1.5)	50 (38-63)	47 (35-58)	1.3 (1.2-1.4)	76.9 (71.4-83.3)

* Composite of first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. Derived from the Optum Research Database for all outcomes except total (first and recurrent) events.

** First and recurrent events. Observed event rates are estimated from the placebo arm in the REDUCE-IT USA trial (Supplemental Figure 6 of the publication⁸; i.e., 679/1598 = 42.5%).

CI: confidence interval; NHANES: National Health and Nutrition Examination Survey; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; UR: uncertainty range

annually could be prevented (UR \$1.3-\$2.2 billion; Table 4). With one year of IPE treatment, 97,000 total (first and recurrent) events could be prevented, averting \$3.4 billion in event costs annually (UR \$2.5-\$4.2 billion).

The estimated outpatient medical costs per REDUCE-IT eligible person were \$6,877, projecting to an annual estimated outpatient medical burden of \$24.8 billion for the entire REDUCE-IT eligible US population (Supplemental Table S6). For indirect costs, the estimated annual indirect cost burden per person were \$6,318, which would project to \$22.7 billion for the entire REDUCE-IT eligible population.

3. Discussion

We estimated that treating all 3.6 million REDUCE-IT eligible US adults with IPE for five years in addition to contemporary medical therapy could prevent 212,000 first and 490,000 total (first and recurrent) ASCVD events. In the current analysis, nonfatal strokes and coronary revascularizations were the most common ASCVD events that would be prevented overall. We further found that the subgroup with the greatest projected benefit (i.e., lowest five-year NNT) was the estimated 2.8 million eligible individuals with eGFR <60 mL/min/1.73m² (NNT 8.9), underscoring the findings of the recent REDUCE-IT RENAL analyses showing the greatest relative and absolute risk reduction in the primary composite endpoint among patients with an eGFR <60 mL/min/1.73m² at baseline [26]. Assuming a daily treatment cost of \$4.59, treating all REDUCE-IT eligible adults with IPE for one year would potentially cost \$6.0 billion but could save an annual \$1.7 billion in first ASCVD event costs, and \$3.4 billion in total (first and recurrent) ASCVD event costs.

As new treatments are developed and marketed, the cost of therapy

becomes an important factor for patients and decision-makers. The current analysis estimated that it would cost \$6.0 billion annually in IPE medication costs to treat all REDUCE-IT eligible US adults. Another analysis which applied a more extensive set of the REDUCE-IT eligibility criteria to NHANES 2009-2014 found that treating an estimated 2.9 million REDUCE-IT eligible US adults would cost \$8.5 billion annually, based on a monthly cost of \$242.32 (~\$8.08 daily) derived from GoodRx® retail prices in 2018 [27]. In the CLARIFY and REACH registries, two large, international, prospective cohorts of participants with or at high risk for coronary artery disease, 15.5% and 11.3%, respectively, were found to be REDUCE-IT eligible [28,29]. Our study had lower proportion of REDUCE-IT eligible patients in NHANES and the ORD (0.4% and 3.9%, respectively) due to our broader study populations including those without ASCVD or at low risk for ASCVD, representative of US population cohorts. Applying the observed event rates in each arm of the REDUCE-IT trial, another analysis of NHANES 1999-2016 concluded that 71,391 primary composite outcome events could be prevented, [30] much larger than our annual estimate of 50,108 using real-world event rates and US-specific effect estimates. However, in the current analysis, the five-year observed composite event rate in the ORD was 19.0%, which was less than the five-year event rate of 24.7% in the REDUCE-IT USA usual care group. Because the ORD cohort of this analysis could be considered to be lower risk than the REDUCE-IT population, it is possible that we underestimated the event rates, costs, and potential cost offsets with IPE treatment associated with more-frequent medical treatment and events that would be expected in a higher-risk population. Although the estimates of widespread IPE therapy are high, the cost-effectiveness literature exploring the value that IPE therapy provides, not only to health outcomes but to patient-centered quality of life, demonstrates that IPE is a cost-effective

Table 3

Annual cost of icosapent ethyl treatment among REDUCE-IT eligible US adults, overall and by subgroups.

Subgroup	REDUCE-IT eligible US adults in millions, NHANES (95% CI)	Annual cost of IPE treatment for all REDUCE-IT eligible US adults in billions of USD (UR)		
		SSR Health \$4.59/day	WAC \$11.48/day	Cost accounting for non-adherence (80% of SSR Health*) \$3.67/day
Overall	3.6 (2.8-4.5)	6.0 (4.7-7.5)	15.1 (11.7-18.9)	4.8 (3.8-6.0)
Cardiovascular Risk Stratum				
Primary Prevention	1.7 (1.3-2.1)	2.8 (2.2-3.5)	7.1 (5.4-8.8)	2.3 (1.7-2.8)
Secondary Prevention	1.9 (1.2-2.7)	3.2 (2.0-4.5)	8.0 (5.0-11.3)	2.5 (1.6-3.6)
Ezetimibe use				
Yes	0.1 (0.03-0.2)	0.2 (0.1-0.3)	0.4 (0.1-0.8)	0.1 (0.0-0.3)
No	3.5 (2.6-4.4)	5.9 (4.4-7.4)	14.7 (10.9-18.4)	4.7 (3.5-5.9)
Baseline diabetes				
Present	2.3 (1.8-2.9)	3.9 (3.0-4.9)	9.6 (7.5-12.2)	3.1 (2.4-3.9)
Absent	1.3 (0.7-1.9)	2.2 (1.2-3.2)	5.4 (2.9-8.0)	1.7 (0.9-2.5)
Baseline eGFR				
<60 mL/min/1.73m ²	2.8 (2.0-3.6)	4.7 (3.4-6.0)	11.7 (8.4-15.1)	3.8 (2.7-4.8)
60-89 mL/min/1.73m ²	0.4 (0.1-0.6)	0.7 (0.2-1.0)	1.7 (0.4-2.5)	0.5 (0.1-0.8)
≥90 mL/min/1.73m ²	0.4 (0.1-0.8)	0.7 (0.2-1.3)	1.7 (0.4-3.4)	0.5 (0.1-1.1)
Baseline TG				
<150 mg/dL	0.8 (0.3-1.4)	1.3 (0.5-2.3)	3.4 (1.3-5.9)	1.1 (0.4-1.9)
≥150 mg/dL	2.8 (2.1-3.5)	4.7 (3.5-5.9)	11.7 (8.8-14.7)	3.8 (2.8-4.7)

* Cost reduced by 20% to account for estimated 6% reduction in adherence observed in the REDUCE-IT trial.⁹

CI: confidence interval; eGFR: estimated glomerular filtration rate; IPE: icosapent ethyl; NHANES: National Health and Nutrition Examination Surveys; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial; TG: triglycerides; UI: uncertainty interval; USD: United States Dollars; WAC: wholesale acquisition cost

Numbers are means. Costs are calculated among patients who had one year of follow-up or died within one year of follow-up.

measure to reduce ASCVD risk among statin-treated patients with hypertriglyceridemia [9,31–33]. Implementation and pragmatic estimates in real-world settings are needed to inform the feasibility of IPE penetration into the eligible patient market.

In this analysis, we did not estimate direct costs for rehabilitation or skilled nursing stays, or the impact of IPE on outpatient medical costs or indirect costs. Indirect costs, which quantify in dollars the money lost to society by an illness, are difficult to estimate. Examples include lost wages due to loss of productivity, transportation to and from medical care, and changes in lifestyle choices after an illness (e.g., diet), family

and professional caregiving, among others. The indirect cost inputs used in the current study (\$6,318/person) include loss of wages from not working and home productivity loss from morbidity and premature mortality. The total indirect costs estimated in this study for the entire REDUCE-IT eligible population were \$22.7 billion annually. Comparatively, the annual net burden of \$4.3 billion to prevent first events (and net cost of \$2.6 billion to prevent total events) for IPE treatment of all eligible individuals is relatively small. If even 5% of outpatient and indirect costs are prevented with one year of treatment, then IPE is a cost-saving therapy. Preventive care, although costly, is a crucial component of the Surgeon General's National Prevention Strategy to improve population health [34].

The strengths of this analysis include the use of NHANES and the ORD, both of which contain a rich set of variables and allowed calculation of nationally-representative estimates. Our findings are the first to report the projected costs saved due to events averted with IPE therapy. Further, we accounted for the competing risk of all-cause death and completed a sensitivity analysis to explore our cost input. Nonetheless, the current findings should be interpreted within the context of known limitations. The abridged set of eligibility criteria applied to the cohorts in this study likely over-estimates the reported population sizes; however, the FDA approval criteria of IPE are much broader than the criteria applied in the current analysis, so we believe our estimates are similar if not conservative to the true population size who may be eligible for treatment. The calculation of estimated treatment effects in the real-world populations assumes that the baseline characteristics and trial-reported effects would be similar among real world cohorts, which we know had some differences in baseline risk factors and demographics compared to the REDUCE-IT USA cohort. The SSR Health cost for IPE of \$4.59/day was used for the primary analysis, but the projected cost estimates would change if a lower cost were available to the patient through copay assistance programs, provider-supplied samples, or other medication cost-reducing measures. The event estimates are derived from the National Inpatient Sample, which incorporates most major third-party payers, and event costs may vary greatly depending on the insurance company reimbursement. All estimates of baseline characteristics and ASCVD events in ORD are subject to the individual limitations of the algorithms used to administratively query the data.

In conclusion, the current analysis shows that if our estimated 3.6 million REDUCE-IT eligible US adults were treated for five years with IPE, 212,000 first events and 490,000 total ASCVD events could be prevented. We estimate that one year of IPE treatment for all eligible US adults would cost the health care system \$6.0 billion but save \$1.8 billion due to first ASCVD events prevented, for a net cost of \$4.2 billion. Annually, \$3.4 billion from preventing 97,000 total events (first and recurrent) could be saved, resulting in a net burden of \$2.6 billion for one year of IPE therapy. Outpatient and indirect costs likely outweigh much of the net cost of IPE therapy.

CRedit authorship contribution statement

Catherine G. Derington: Conceptualization, Methodology, Writing – original draft, Visualization, Project administration. **Adam P. Bress:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision, Project administration, Funding acquisition. **Jennifer S. Herrick:** Formal analysis, Writing – review & editing, Visualization. **Wenjun Fan:** Formal analysis, Data curation, Writing – review & editing. **Nathan D. Wong:** Resources, Writing – review & editing, Supervision, Project administration. **Katherine E. Andrade:** Methodology, Writing – review & editing, Project administration. **Jonathan Johnson:** Methodology, Formal analysis, Data curation, Writing – review & editing, Project administration. **Sephy Philip:** Writing – review & editing, Supervision, Project administration. **David Abrahamson:** Writing – review & editing. **Lixia Jiao:** Writing – review & editing. **Deepak L. Bhatt:** Writing – review & editing. **William S. Weintraub:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision,

Table 4

Annual cost saved due to events prevented with icosapent ethyl treatment in all REDUCE-IT eligible US adults, overall.

Outcome	Observed one-year composite event rates		Predicted one-year ASCVD event rates if treated with icosapent ethyl		Events prevented with one year of IPE treatment, thousands (95% CI)	Mean cost of one event* (95% CI)	Annual cost of events prevented, rounded to the nearest tenth of one billion (UR)
	% (95% CI)	Total number per year, thousands (95% CI)	% (95% CI)	Total number per year, thousands (95% CI)			
Primary composite outcome**							
First events only	4.5 (4.3-4.7)	162 (123-201)	3.1 (3.0-3.2)	112 (85-138)	50 (39-62)	\$32,980 (\$20,619-\$45,341)	\$1.8 (\$1.3-\$2.2)
Total events [†]	8.5 (7.9-9.1)	306 (238-383)	5.8 (5.4-6.2)	209 (157-260)	97 (73-121)	\$32,980 (\$20,619-\$45,341)	\$3.4 (\$2.5-\$4.2)
Cardiovascular death	0.7 (0.6-0.8)	25 (18-32)	0.5 (0.4-0.5)	18 (13-23)	7 (6-9)	\$31,058 (\$30,110-\$32,006)	\$0.2 (\$0.2-\$0.3)
Nonfatal myocardial infarction	1.2 (1.1-1.3)	43 (32-54)	0.9 (0.8-0.9)	32 (25-40)	11 (8-13)	\$28,428 (\$28,153-\$28,702)	\$0.3 (\$0.3-\$0.4)
Nonfatal stroke	1.0 (0.9-1.1)	36 (27-45)	0.6 (0.6-0.7)	22 (16-27)	14 (11-18)	\$20,615 (\$20,315-\$20,914)	\$0.3 (\$0.2-\$0.4)
Coronary revascularization	2.0 (1.9-2.2)	72 (54-90)	1.3 (1.2-1.4)	47 (35-58)	25 (19-31)	\$44,147 (\$43,600-\$44,693)	\$1.2 (\$0.9-\$1.4)
Unstable angina	0.7 (0.6-0.8)	25 (18-32)	0.4 (0.3-0.4)	14 (11-18)	11 (8-13)	\$28,464 (\$28,175-\$28,753)	\$0.3 (\$0.3-\$0.4)

CI: confidence interval; IPE: icosapent ethyl; REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; UI: uncertainty range

*Event costs are estimated from the National Inpatient Sample per Weintraub et al.⁹ For the mean cost of one primary composite outcome event, a weighted average of the individual components, based on the observed event rates, was calculated.

** Composite of first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

[†]First and recurrent events. Observed event rates are estimated from the REDUCE-IT USA trial, not the Optum Research Database.

Project administration, Funding acquisition.

Declaration of Competing Interest

Dr. Catherine Derington receives research funding to her institution from Amarin Pharma, Inc. **Dr. Adam Bress** receives research support to his institution from Amarin and private consulting from Amarin. **Dr. Nathan Wong** has received research support to his institution from Amarin Pharma, Inc., Amgen, Esperion, and Novartis, is a consultant for Novartis, and has participated on an advisory boards with Amarin Pharma, Amgen, and speakers bureaus for Esperion and Amarin Pharma, Inc. **Dr. Deepak L. Bhatt** is the Chair and PI of REDUCE-IT and discloses the following relationships - Advisory Board: Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org); Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), 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), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, 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), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda. **Dr. William Weintraub** received research support from Amarin Pharma, Inc. and from the National Institutes of Health. He provides consulting to Amarin Pharma, Inc., AstraZeneca, Janssen, SC

Pharma, and The Medicines Company. **Drs. David Abrahamson, Lixia Jiao, and Sephy Philip** are employed by Amarin Pharma, Inc. **Katherine Andrade, MPH and Jonathan Johnson, MS** are employees of Optum, which received funding from Amarin Pharma, Inc. for the conduct of the study. **All other authors** have no relationships to disclose.

Role of the funding source

This research was supported by an academic-industry partnership with Amarin Pharma, Inc. The sponsor had input on the study design and writing the report. The collection, analysis, and interpretation of data and decision to submit the article for publication was made by the authors.

Acknowledgements

The authors wish to thank the investigators, the study coordinators, and participants of the REDUCE-IT trial.

Sources of Funding

The study was supported by a research grant from Amarin Pharma, Inc., which was involved in the study design and interpretation of data, and development and review of this article. The decision to submit the article for publication was made by the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ajpc.2022.100345](https://doi.org/10.1016/j.ajpc.2022.100345).

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