REDUCE-IT Eligibility and Preventable Cardiovascular Events in the US Population (from the National Health and Nutrition Examination Survey [NHANES])

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The reduction of cardiovascular events with icosapent ethyl−intervention (REDUCE-IT) trial showed in persons with prior cardiovascular disease (CVD) or diabetes mellitus (DM) that icosapent ethyl (IPE) reduced CVD events by 25%. We projected the preventable initial and total CVD events if REDUCE-IT trial eligibility criteria were applied to US adults. We identified US adults with available REDUCE-IT inclusion criteria from NHANES Surveys 1999-2016 and estimated primary (CVD death, nonfatal myocardial infarction, stroke, revascularization, or unstable angina) and secondary composite (CVD death, nonfatal MI or stroke) events using REDUCE-IT published event rates in the IPE and placebo groups, the difference being the number of preventable events. From 11,445 adults aged ≥45 years (representing 111.1 million [M]), a total of 319 persons (3.0 M) fit key REDUCE-IT eligibility criteria: triglycerides of 135 to 499 mg/dL, HbA1c <10%, blood pressure <200/100 mm Hg, and on a statin with LDL-C of 40 to 99 mg/dL. 63% had prior CVD and 37% had DM + ≥1 risk factor (primary prevention cohort). If these persons are given IPE for the REDUCE-IT median trial period of 4.9 years, we estimated preventing a total 349,817 (71,391/year) primary CVD outcomes of which 146,011 (29,798/year) were initial events. Most (24,151) preventable events were from the secondary prevention cohort. Using FDA eligibility criteria, an estimated 4.6 million persons would be eligible for IPE, with 60,544 preventable primary CVD outcomes annually from REDUCE-IT USA event rates. In conclusion, many CVD events in US adults with known CVD or DM and well-controlled LDL-C on statin therapy can be prevented with IPE. **(Am J Cardiol 2020;134:62−68)**

The reduction of cardiovascular events with icosapent ethyl−intervention (REDUCE-IT) trial,[1] preceded by the Japan EPA Lipid Intervention Study (JELIS) trial done in Japan[2] are the only clinical trials to show benefit in reducing atherosclerotic cardiovascular disease (ASCVD) events beyond statin therapy. JELIS involved treatment with 1.8 g/day of pure EPA, but had higher mean plasma EPA levels in participants and lower statin dosages than typically used in the United States; however, there was a significant 19% reduction in CVD events. The REDUCE-IT trial showed a 25% and 30% reduction in initial and total events of the primary composite end point of ASCVD events, respectively, with 4 g/day of IPE in persons with either ASCVD or diabetes mellitus (DM) and additional risk factors who had triglycerides of 135 to 499 mg/dL and well-controlled LDL-C on a statin.[1,3] Significant reductions were also demonstrated for a many secondary end points. Prescription IPE (Vascepa) was recently approved by the Food and Drug Administration (FDA) for the reduction of CVD events in persons with known ASCVD or DM with risk factors on maximally tolerated statin therapy with triglycerides of ≥150 mg/dl.[4] Not established is the number of US adults who could potentially benefit from IPE based on REDUCE-IT eligibility criteria or FDA indications, and the number of potentially preventable ASCVD events. We estimated the number of US adults potentially eligible for IPE, and more importantly the number of ASCVD events that could be prevented with its use.

Methods

We identified US adults aged 20 years and over with available REDUCE-IT inclusion criteria using data from National Health and Nutrition Examination Survey (NHANES) 1999-2016. NHANES is a population-based cross-sectional evaluation of noninstitutionalized US individuals with biennial examinations from 1999 to present. This survey collects information regarding participants' demographic characteristics, medical history, clinical examination, laboratory tests, and prescription medication.

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Details regarding NHANES methodology have been described previously.[5]

Specific REDUCE-IT eligibility criteria utilized in our study included fasting triglycerides of 135 to 499 mg/dL, hemoglobin A1c (HbA1c <10%), blood pressure <200/100 mmHg and already on statin treatment with LDL-C between 40 and 99 mg/dL. The specific inclusion criteria for primary prevention cohort (those without prior ASCVD) were (1) diabetes mellitus (type 1 or type 2) requiring treatment with medication and (2) men and women aged 50 years or over and at least one of the following additional risk factors for CVD: men ≥55 years of age or women ≥65 years of age, cigarette smoker or stopped smoking for at least 3 months, hypertension (defined as blood pressure ≥ 140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication, HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women, or microalbuminuria defined as albumin/creatinine ratio ≥2.5 mg/mol. Inclusion criteria available in NHANES for the secondary prevention cohort were self-reported diagnosis of coronary heart disease, heart attack or stroke (information regarding carotid or peripheral arterial diseases or revascularization were not available). In a secondary analysis, we further calculated the eligible population based on the label approved by the US Food and Drug Administration for IPE: (1) Adults aged 18 and over with elevated triglyceride level (≥150 mg/dL) (2) have either established ASCVD or DM with 2 or more additional risk factors as mentioned above, and (3) statin therapy, but without specified LDL-C inclusion levels.

We first identified IPE eligible US adults according to the aforementioned criteria and summarized demographic characteristics and risk factor distributions in comparison to participants in the placebo group from REDUCE-IT and REDUCE-IT USA trial. Next, we estimated the number of anticipated ASCVD events including primary composite end points (cardiovascular death, nonfatal MI, stroke, revascularization, or unstable angina) and secondary composite end point (cardiovascular death, nonfatal MI, or stroke) as well as individual secondary endpoints including (cardiovascular death, revascularization, nonfatal MI, stroke, and total mortality using overall REDUCE-IT initial[1] and total[3] published event rates as well as REDUCE-IT USA event rates (for initial events only)[6] in the IPE and placebo groups, respectively, with the difference being the number of preventable events. We finally repeated the analysis based on the slightly modified US FDA eligibility criteria utilizing REDUCE-IT USA event rates as described above. NHANES sample weighting was utilized to project estimates to the US population. Both total preventable events based on the REDUCE-IT follow-up period, as well as annualized preventable events are presented. SAS statistical software (SAS Institute, Cary, NC) was used for analyses.

Results

A total of 53,348 US adults were identified in our 16 years of NHANES datasets, 21,548 (representing a sample weighted population of 222.2 million) were randomly assigned to morning sessions (with the requirement of fasting for at least 8.5 hours). After applying other exclusion criteria as available in NHANES, including those aged below 45 years old, fasting TG <135 mg/dL or ≥500 mg/dL, HbA1c >10%, SBP ≥200 mm Hg or DBP ≥100 mm Hg, LDL-C outside the range of 40 to 100 mg/dL and not on statin treatment, we identified 319 subjects representing a sample weighted population of 3.0 million US adults who fit REDUCE-IT trial eligibility criteria. Of these, 63% had prior ASCVD (secondary prevention cohort) and 37% had DM and additional risk factors (primary prevention cohort) (Figure 1).

Table 1 displays the demographic and clinical factors comparison between our REDUCE-IT eligible US adults in NHANES and the REDUCE-IT placebo group. When compared with the overall placebo group, our eligible sample had a higher proportion of persons aged ≥65 years, fewer men and Caucasians, lower TG levels, and a higher proportion of subjects belonging to the primary prevention cohort. When compared with the REDUCE-IT USA placebo group, our eligible sample had very similar characteristics except for lower TG levels as well.

Figure 2 and Table 2 show the estimated number initial and total primary and secondary composite outcomes based on our REDUCE-IT eligible sample. If given IPE for 4.9 years, from sample weighted projections we estimate a total of 71,391/year primary and 31,660/year secondary ASCVD outcomes (total events, including initial and recurrent events) could be prevented, of which, 29,798/year and 22,349/year were first events, respectively. Table 2 additionally shows the annual preventable events for the individual secondary endpoints from REDUCE-IT. Table 3 stratifies results for the primary and secondary composite endpoints according to belonging to the primary or secondary prevention cohort in REDUCE-IT, demonstrating that the vast majority of preventable events would occur from eligible secondary prevention subjects. If based on REDUCE-IT USA event rates (initial events only), we estimate preventing 40,351/year primary composite and 27,936/year secondary composite ASCVD outcomes in the United States (Table 4 and Figure 3).

Supplementary Figure 1 displays the sample selection procedure based on modified inclusion criteria from the USA FDA label on IPE. A total of 476 subjects, projected to 4.6 million, in the United States were identified in our NHANES 1999-2016 sample as being eligible for IPE based on the FDA label. An estimate of 60,544 and 41,915 events per year for primary and secondary composite end points, respectively, were expected to be prevented if these persons were treated with IPE. The estimated preventable events for key individual secondary end points of cardiovascular death, MI, and stroke were 18,628, 19,561, and 17,698, respectively. In addition, a total of 24,217 all-cause deaths were also determined to be preventable annually with IPE treatment, based on the USA data from REDUCE-IT (Supplementary Figure 2). Moreover, individual preventable events for selected secondary endpoints are provided in Supplementary Table 1.

Discussion

We estimate that at least 3.0 million US adults would be eligible for IPE therapy based on REDUCE-IT eligibility criteria, with approximately 4.5 million eligible based on

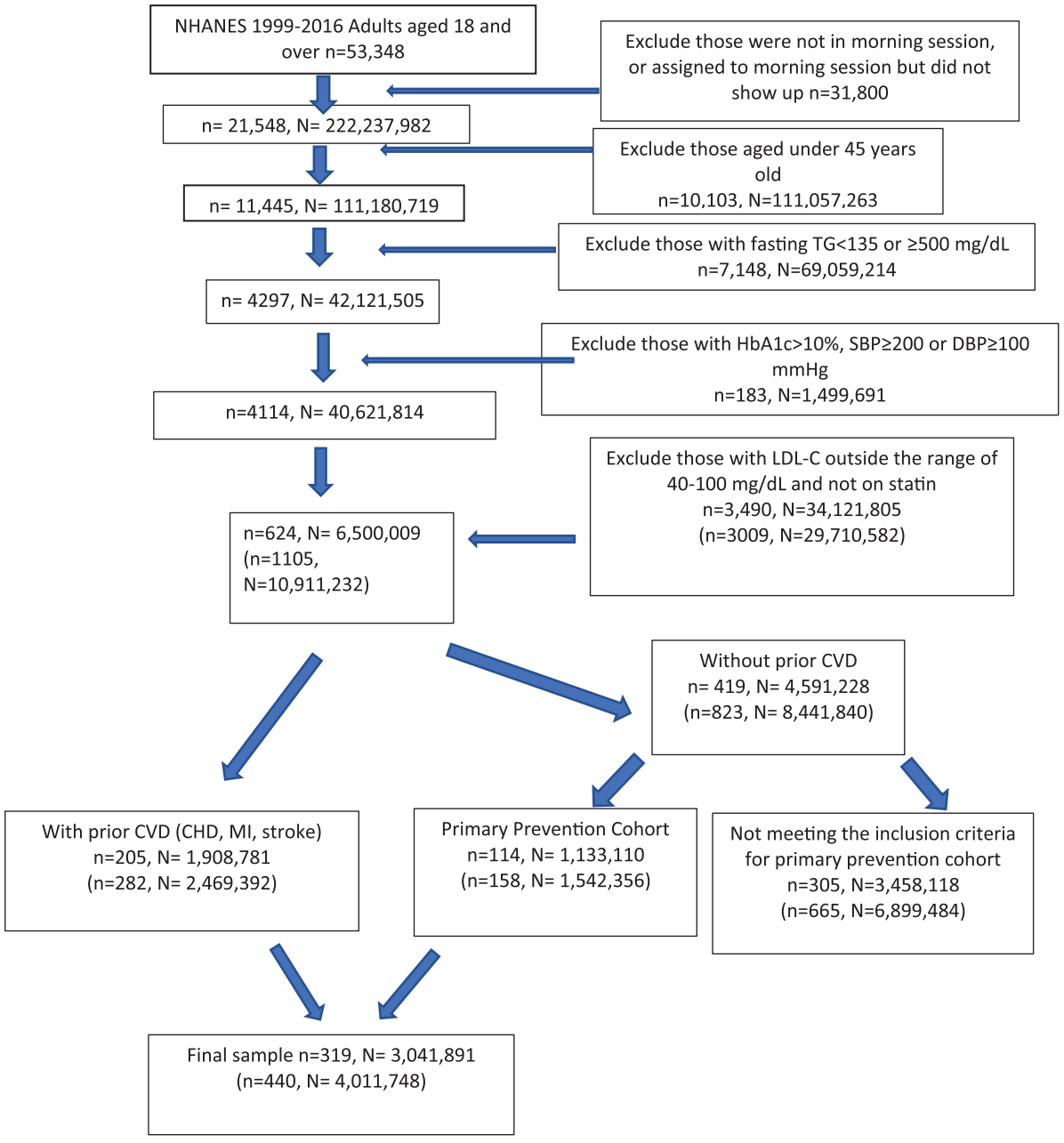

Figure 1. Sample selection flowchart for REDUCE-IT eligible population in NHANES 1999-2016. *Primary prevention cohort inclusion criteria:
1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One of the following additional risk factor for CVD:
- Men ≥55 years of age and Women ≥65 years of age;
- Cigarette smoker or stopped smoking for at least 3 months;
- Hypertension (blood pressure ≥140 mm Hg systolic OR ≥90 mm Hg diastolic) or on antihypertensive medication;
- HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women;
- Micro- or macroalbuminuria. Microalbuminuria is defined as albumin/creatinine ratio ≥2.5 mg/mmol

Numbers in parenthesis indicated subjects meet all other inclusion/exclusion criteria regardless of statin use.

FDA indications. Moreover, >70,000 total ASCVD events could be prevented annually (including nearly 30,000 initial events); approximately 90% of these preventable events are among those with pre-existing ASCVD. In addition, FDA indications expand the potentially eligible persons and preventable events by approximately 50%, and use of REDUCE-IT USA event rates result in a greater number of projected preventable events due to a higher risk population (>40,000 initial events prevented annually). Our analysis further extends the findings of the REDUCE-IT trial by estimating the number of US adults potentially eligible for IPE based on the REDUCE-IT entry criteria, as well as by more recent FDA indications. In addition, we estimate the preventable ASCVD events from the REDUCE-IT published

Table 1
Demographic characteristics among icosapent ethyl eligible subjects from NHANES 1999-2016, as compared with REDUCED-IT overall and USA placebo groups

Variable	NHANES (n=319, N= 3,041,891)	REDUCED-IT placebo (n=4,090)	REDUCE-IT USA placebo (n=1,598)
Age (years)			
Median (IQR)	65.4 (60.2-72.2)	64.0 (57.0-69.0)	65.0 (59.0-71.0)
≥65 ((n) (weighted)	207 (N=1,703,079, 56.0%)	1906 (46.6%)	866 (54.2%)
Men (weighted)	205 (N=1,819,563, 59.8%)	28995 (70.8%)	1070 (67.0%)
Whites race (weighted)	201 (N=2,566,577, 84.4%)	3688 (90.2%)	1474 (92.2%)
Body mass index (kg/m^2)			
Median (IQR)	31.2 (28.2-36.0)	30.8 (27.9-34.7)	32.2 (28.7-36.6)
≥30 (n) (weighted)	178 (N=1,874,264, 61.6%)	2362 (57.8%)	1053 (65.9%)
Cardiovascular risk stratum (n) (weighted)			
Secondary prevention cohort	205 (N=1,908,781, 62.7%)	2893 (70.7%)	942 (58.9)
Primary prevention cohort	114 (N=1,133,110, 37.3%)	1197 (29.3%)	656 (41.1)
Diabetes (n) (weighted)			
Type 1	5 (N=44,873, 1.4%)	30 (0.7%)	20 (1.3)
Type 2	217 (N=2,055,414, 67.6%)	2363 (57.8%)	1095 (68.5)
No diabetes	97 (N=941,604, 31.0%)	1694 (41.4%)	483 (30.2%)
Data missing	0	3 (0.1%)	0
Median triglyceride level (IQR) (mg/dL)	180.6 (154.6-222.5)	216.0 (175.5-274.0)	217.5 (175.0-273.5)
Median HDL cholesterol level (IQR) (mg/dL)	42.1 (35.0-49.9)	40.0 (35.0-46.0)	40.0 (34.5-46.5)
Median LDL cholesterol level (IQR) (mg/dL)	77.1 (65.1-89.9)	76.0 (63.0-89.0)	73.0 (61.0-85.0)
Distribution of triglyceride levels (mg/dL) − (n) (weighted N, %)			
<150	62 (N=545,058, 17.9%)	429/4089 (10.5%)	172 (10.8%)
≥150 to < 200	146 (N=1,400,358, 46.0%)	1191/4089 (29.1%)	446 (27.9%)
≥ 200	111 (N=1,096,475, 36.1%)	2469/4089 (60.4%)	979 (61.3%)
Triglyceride level ≥ 200 mg/dL and HDL cholesterol ≤35 mf/dL − no. (weighted N, %)	33 (N=355,427, 11.7%)	794 (19.4%)	349 (21.8%)

Numbers are displayed as weighted median or frequency with projected population and weighted percentage.

event rates, overall and among those subjects enrolled in the United States. These eligibility data are somewhat similar to recent data from Europe which show 15% of patients being eligible for IPE, although the patient population was more limited to those with stable coronary artery disease.[7]

Although clinical trials with statins show an approximately 30% to 40% reduction in ASCVD events, many events still occur, a reflection of "residual risk."[8] The IMPROVE-IT trial with ezetimibe was the first among nonstatin therapies to demonstrate incremental reduction of risk beyond statin therapy, albeit in a very high-risk patient population (e.g., acute coronary syndrome within 10 days).[9] This was followed by 2 major clinical trials of proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors showing 15% relative risk reductions beyond statin therapy for persons with a recent acute coronary syndrome (in the case of alirocumab)[10] or stable atherosclerotic CVD (in the case of evolocumab).[11] The REDUCE-IT trial[1] was the first multinational trial to involve a pure, stable, prescription

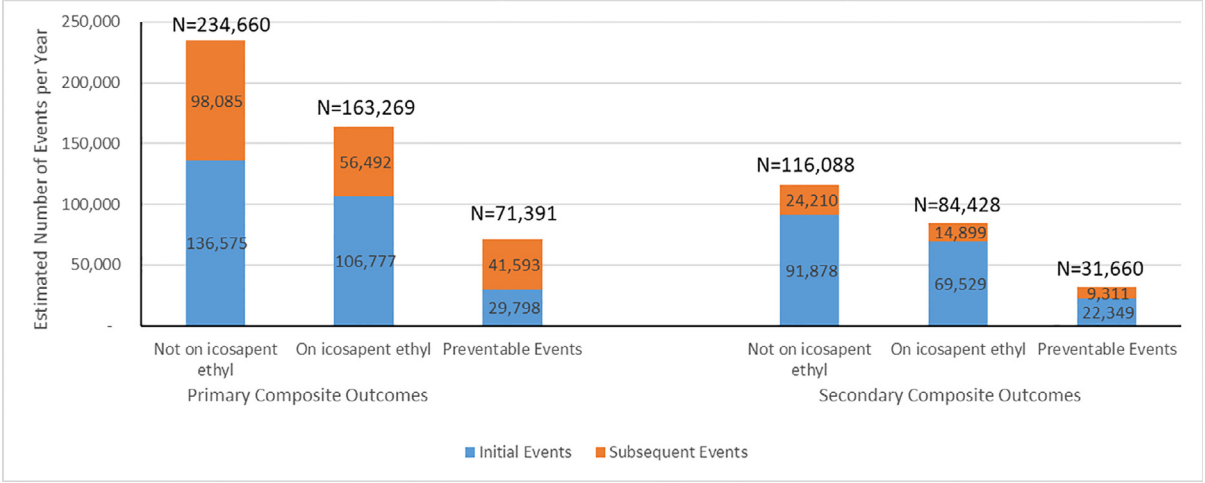

Figure 2. Distribution of annual projected initial and subsequent preventable primary and secondary composite end point events in the United States if on icosapent ethyl, NHANES 1999-2016.

Table 2
Weighted number and absolute event rate of expected preventable cardiovascular outcomes if on icosapent ethyl, NHANES 1999-2016 (n = 319 weighted to 3.0 M)

	If not on icosapent ethyl			If on icosapent ethyl			Preventable Events		
Variable	No.	%	Events/year	No.	%	Events/year	No.	%	Events/year
Primary composite	669,216	22.0%	136,575	523,205	17.2%	106,777	146,011	4.8%	29,798
Total Primary composite	1,149,835	37.8%	234,660	800,017	26.3%	163,269	349,817	11.5%	71,391
Key secondary composite	450,200	14.8%	91,878	340,692	11.2%	69,529	109,508	3.6%	22,349
Total secondary composite	568,834	18.7%	116,088	413,697	13.6%	84,428	155,136	5.1%	31,660
Cardiovascular death or nonfatal myocardial infarction	377,194	12.4%	76,978	292,022	9.6%	59,596	85,173	2.8%	17,382
Fatal or nonfatal myocardial infarction	264,645	8.7%	54,009	185,555	6.1%	37,868	79,089	2.6%	16,141
Urgent or emergency revascularization	237,267	7.8%	48,422	161,220	5.3%	32,902	76,047	2.5%	15,520
Cardiovascular death	158,178	5.2%	32,281	130,801	4.3%	26,694	27,377	0.9%	5,587
Hospitalization for unstable angina	115,592	3.8%	23,590	79,089	2.6%	16,141	36,503	1.2%	7,450
Fatal or nonfatal stroke	100,382	3.3%	20,486	73,005	2.4%	14,899	27,377	0.9%	5,587
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	514,080	16.9%	104,914	407,613	13.4%	83,186	106,466	3.5%	21,728
*Death from any cause	231,184	7.6%	47,180	203,807	6.7%	41,593	27,377	0.9%	5,587

Eligible sample from NHANES 1999-2016 was 319 (projected to 3,041,891 people). Numbers are displayed as the population weighted sample size based on a median follow-up time of 4.9 years. Absolute event rate of expected CVD and event/person year was based Figure 4 from Bhatt et al.[4]
* Indicates end point that was not statistically significant in the main trial.

Table 3
Weighted number and absolute initial event rate of expected preventable cardiovascular outcomes if on icosapent ethyl stratified by risk category, NHANES 1999-2016

	If not on icosapent ethyl			If on icosapent ethyl			Preventable Events		
	No.	%	Events/year	No.	%	Events/year	No.	%	Events/year
***Primary Prevention Cohort (n=114, N= 1,133,110)**									
Primary Composite	154,103	13.6%	31,450	138,239	12.2%	28,212	15,864	1.4%	3,238
Secondary Composite	111,045	9.8%	22,662	92,915	8.2%	18,962	18,130	1.6%	3,670
Secondary Prevention Cohort (n=205, N= 1,908,781)									
Primary Composite	486,739	25.5%	99,334	368,385	19.3%	75,183	118,344	6.2%	24,151
Secondary Composite	322,584	16.9%	65,833	238,598	12.5%	48,693	83,986	4.4%	17,140

Numbers are displayed as the population weighted sample size.
* Indicates subgroup not statistically significant for primary or secondary composite outcomes from the original trial published by Bhatt et al,[4] in subgroup analyses.

Table 4
Weighted first preventable primary and secondary composite end point events if on icosapent ethyl based on REDUCE-IT USA outcome, NHANES 1999-2016

	If not on icosapent ethyl			If on icosapent ethyl			Preventable Events		
	No.	%	Events/year	No.	%	Events/year	No.	%	Events/year
Primary composite	751,347	24.7	153,336	553,624	18.2	112,985	197,723	6.5	40,351
Key secondary composite	504,954	16.6	103,052	368,069	12.1	75,116	136,885	4.5	27,936
Cardiovascular death or nonfatal myocardial infarction	422,823	13.9	86,290	313,315	10.3	63,942	109,508	3.6	22,348
Fatal or nonfatal myocardial infarction	267,686	8.8	54,630	203,807	6.7	41,593	63,880	2.1	13,037
Urgent or emergency revascularization	273,770	9.0	55,871	185,555	6.1	37,868	88,215	2.9	18,003
Cardiovascular death	203,807	6.7	41,593	142,969	4.7	29,177	60,838	2	12,416
Hospitalization for unstable angina	133,843	4.4	27,315	76,047	2.5	15,520	57,796	1.9	11,795
Fatal or nonfatal stroke	124,718	4.1	25,453	79,089	2.6	16,141	45,628	1.5	9,312
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	587,085	19.3	119,813	434,990	14.3	88,774	152,095	5	31,039
Death from any cause	298,105	9.8	60,838	219,016	7.2	44,697	79,089	2.6	16,141

Numbers are displayed as the population weighted sample size.

formulation of eicosapentanoic acid, showing 25% and 30% relative risk reductions for initial and total events of the primary composite ASCVD end point in persons with known ASCVD or DM and additional risk factors. Of note, the benefit was independent of baseline or on-treatment triglyceride level achieved (≥150 mg/dL vs <150 mg/dL), suggesting that the risk reduction may be due to mechanisms other than triglyceride reduction.[12] Thus, residual hypertriglyceridemia may identify a population of patients that may benefit from evidence-based therapies such as

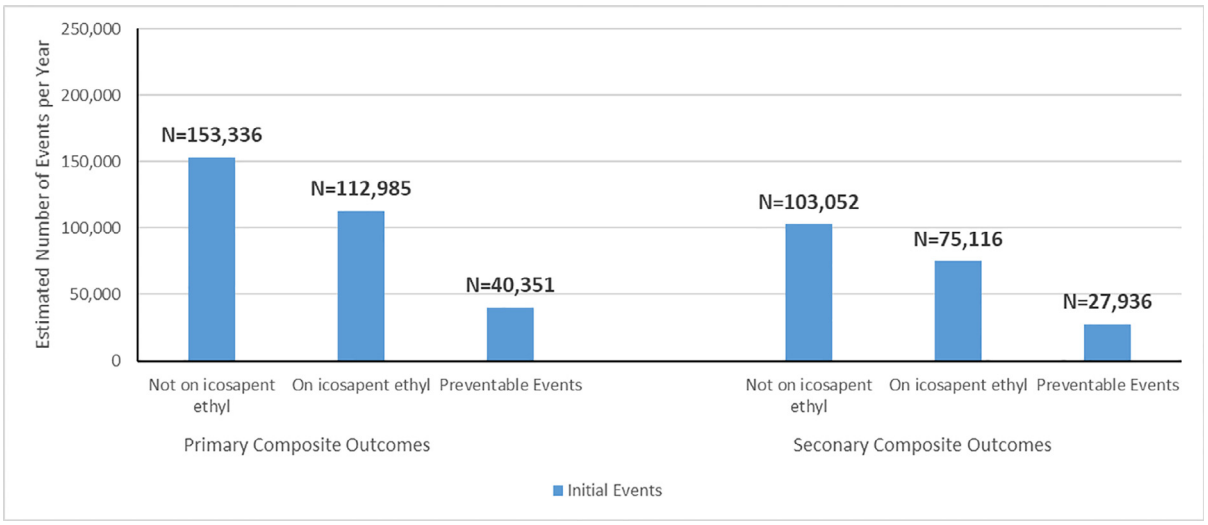

Figure 3. Distribution of annual projected initial and subsequent preventable primary and secondary composite end point events if on icosapent ethyl based on REDUCE-IT USA outcomes, NHANES 1999-2016

IPE. Although a mineral oil placebo was used in REDUCE-IT, the FDA concluded that this was unlikely to have any significant impact on the results of the trial.[13] Moreover, the results of other recent trials, including the STRENGTH trial,[14] which had used a combination of EPA and DHA and/or had different dosages of EPA or different inclusion criteria, cannot be compared with REDUCE-IT.

Our study has a number of strengths and limitations. The NHANES cohort is particularly well-suited for this type of analysis due to the standardized assessment of risk factors and other eligibility criteria as well as the sample weights that are applied to project to the greater and ethnically diverse US population. However, NHANES is limited to self-reported information on ASCVD history, and does not have a number of other ASCVD eligibility criteria, namely information on angiographically defined coronary artery disease, history of revascularization, and peripheral arterial disease (ankle brachial index was not available for most of our NHANES surveys used in this analysis) which could result in underestimation of our eligible cohort. Moreover, our estimates for some of the secondary outcomes are based on a small number of actual preventable events estimated due to the relatively small absolute differences in ASCVD events based on the REDUCE-IT trial.

In conclusion, we estimate approximately 3 million US adults would be eligible for IPE with over 70,000 total ASCVD events that could be prevented annually (and nearly 30,000 initial events) based on the REDUCE-IT trial event rates. In addition, with the slightly greater risk reductions seen in REDUCE-IT USA,[6] including significant reductions in total mortality, a greater number of preventable events and deaths would be preventable based on these estimates. Finally, if FDA indications are utilized, eligible individuals and preventable events are increased by approximately 50%. Further studies should address the economic impact of IPE if applied to eligible patients to inform us of appropriate costs to achieve acceptable cost-effectiveness thresholds, as well as long-term benefits not addressed by REDUCE-IT.

Authors' contribution

Dr. Nathan Wong designed the study and wrote the manuscript.

Dr. Wenjun Fan conducted the analysis and provided critical review and revision.

Drs. Toth, Granowitz, and Philip provided critical review and revision.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.015.

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