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ORIGINAL ARTICLE
Lipids

Potential effects of icosapent ethyl on cardiovascular outcomes in cigarette smokers: REDUCE-IT smoking

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Aims Cigarette smoking is among the most well-established risk factors for adverse cardiovascular outcomes. We sought to determine whether icosapent ethyl (IPE), a highly purified form of eicosapentaenoic acid with antiatherothrombotic properties, may reduce the excessive risk of cardiovascular disease (CVD) attributable to smoking.

Methods and results Reduction of Cardiovascular Events with Icosapent Ethyl Trial (REDUCE-IT) was a multinational, double-blind trial that randomized 8179 statin-treated patients with elevated triglycerides and CV risk to IPE or placebo, with a median follow-up period of 4.9 years. Icosapent ethyl reduced the primary composite endpoint [CV death, non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularization, or hospitalization for unstable angina] by 25% ($P < 0.0001$). In the current analyses, the effect of IPE was evaluated in REDUCE-IT using *post hoc* analyses based on smoking history. Groups were classified as current smokers ($n = 1241$), former smokers ($n = 3672$), and never smokers ($n = 3264$). Compared with placebo, IPE use in combined current and former smokers ($n = 4913$) was associated with significant reductions in time to the primary composite endpoint {hazard ratio: 0.77 [95% confidence interval (CI): 0.68–0.87]; $P < 0.0001$} and in total events [rate ratio: 0.71 (95% CI: 0.61–0.82); $P < 0.0001$]. These benefits remained significant when subdivided into current and former smokers ($P = 0.04$, $P = 0.005$), with reductions in the key secondary composite endpoint ($P < 0.0001$) and in the individual components of CV death or non-fatal MI ($P = 0.04$, $P = 0.01$) and fatal or non-fatal MI ($P = 0.009$, $P = 0.01$), respectively. Benefits were consistent and significant in non-smokers as well. Overall, there were similar estimated rates of first occurrences of primary CVD endpoints in current smokers (23.8%) and former smokers (23.0%) assigned to IPE compared with never smokers on placebo (25.7%).

Conclusion In REDUCE-IT, IPE treatment was associated with a reduced risk of CV events in current and former smokers to levels observed in never smokers. While smoking cessation should always be recommended, these data raise the possibility that IPE treatment may attenuate CV hazards attributable to smoking.

Keywords Cigarette smoking • Icosapent ethyl • Hypertriglyceridemia • Reduce-IT • Clinical trial

Introduction

Cigarette smoking is the most preventable cause of cardiovascular disease (CVD), and overall, ~8 million deaths are attributed annually to tobacco-related diseases worldwide.[1] While smoking cessation is the most effective way to reduce CVD events,[2] excessive risk persists despite the efficacy of standard of care (SOC) therapies (e.g. antiplatelet agents, statins) that are unable to eliminate residual thrombogenicity, endothelial dysfunction, oxidative stress, and the pro-inflammatory milieu maintained in active smokers.[3,4] Recently,

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Table 1 Selected baseline characteristics based on smoking status in REDUCE-IT

	Smoking status: current (*N* = 1241)	Smoking status: former (*N* = 3672)	Smoking status: never (*N* = 3264)	Total (*N* = 8177)	*P*-value
Age (years), median (Q1–Q3)	60.0 (54.0–66.0)	65.0 (58.0–70.0)	64.0 (57.0–70.0)	64.0 (57.0–69.0)	<0.0001
Age ≥ 65 years, *n* (%)	370 (29.8%)	1885 (51.3%)	1506 (46.1%)	3761 (46.0%)	<0.0001
Female, *n* (%)	281 (22.6%)	687 (18.7%)	1389 (42.6%)	2357 (28.8%)	<0.0001
BMI (kg/m^2), median (Q1–Q3)	30.2 (27.1–33.8)	31.0 (28.1–34.7)	31.0 (27.8–34.9)	30.8 (27.8–34.6)	<0.0001
BMI ≥ 30 kg/m^2	650 (52.4%)	2183 (59.4%)	1860 (57.0%)	4693 (57.4%)	<0.0001
CV risk category					
Secondary prevention	956 (77.0%)	2827 (77.0%)	2000 (61.3%)	5783 (70.7%)	<0.0001
Primary prevention	285 (23.0%)	845 (23.0%)	1264 (38.7%)	2394 (29.3%)	<0.0001
Type II diabetes, *n* (%)	648 (52.2%)	1974 (53.8%)	2108 (64.6%)	4730 (57.8%)	<0.0001
Laboratory measurements					
Creatinine clearance >30 and <60 mL/min	97 (7.8%)	386 (10.5%)	407 (12.5%)	890 (10.9%)	<0.0001
hs-CRP (mg/L), median (Q1–Q3)	2.7 (1.4–5.8)	2.1 (1.0–4.3)	2.1 (1.0–4.3)	2.2 (1.1–4.5)	<0.0001
Triglycerides (mg/dL), median (Q1–Q3)	224.5 (181.0–284.0)	218.5 (177.5–277.0)	210.5 (172.0–262.0)	216.0 (176.0–272.5)	<0.0001
HDL-C (mg/dL), median (Q1–Q3)	38.5 (33.5–44.0)	40.0 (35.0–45.5)	40.5 (35.5–47.0)	40.0 (35.0–46.0)	<0.0001
LDL-C (mg/dL), median (Q1–Q3)	77.0 (65.0–92.0)	74.5 (61.0–87.0)	75.0 (62.0–89.0)	75.0 (62.0–89.0)	<0.0001
EPA (μg/mL), median (Q1–Q3)	24.9 (16.3–38.0)	27.8 (18.4–41.7)	24.6 (15.7–38.4)	26.1 (17.1–40.0)	<0.0001
Medications taken at baseline, *n* (%)					
Antidiabetic	598 (48.2%)	1826 (49.7%)	1962 (60.1%)	4386 (53.6%)	<0.0001
Antihypertensive	1155 (93.1%)	3535 (96.3%)	3099 (94.9%)	7789 (95.3%)	<0.0001
Antiplatelet	1007 (81.1%)	3034 (82.6%)	2451 (75.1%)	6492 (79.4%)	<0.0001
ACE or ARB	919 (74.1%)	2849 (77.6%)	2571 (78.8%)	6339 (77.5%)	0.003
Beta-blockers	896 (72.2%)	2714 (73.9%)	2172 (66.5%)	5782 (70.7%)	<0.0001
Statin	1236 (99.6%)	3656 (99.6%)	3253 (99.7%)	8145 (99.6%)	0.8

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker, BMI = body mass index.

icosapent ethyl (IPE), a highly purified form of eicosapentaenoic acid (EPA), was shown to reduce CVD events in high-risk men and women with hypertriglyceridaemia (HTG),[5] a lipid disorder characterized by elevated atherothrombotic risk.[6,7] Because EPA reduces platelet aggregation and pro-inflammatory cytokines while improving endothelial function,[8] this study was designed to examine the effect of IPE on atherothrombotic events in cigarette smokers who remain at persistently elevated risk of CVD, despite treatment with effective SOC therapies.

Methods

The Reduction of Cardiovascular Events with Icosapent Ethyl Trial (REDUCE-IT) was a phase 3b, double-blind, placebo-controlled trial of 8179 statin-treated patients with well-controlled low-density lipoprotein cholesterol [median baseline LDL-C, 75 mg/dL (1.94 mmol/L)] and HTG [150–499 mg/dL (1.69–5.63 mmol/L)] who were randomized to 4 g daily of either IPE or placebo (two capsules administered twice daily with meals); protocol and study results have been previously published.[5,9] All sites received approval from their respective institutional review board or ethics committee. The primary endpoint was a composite of CV death, non-fatal MI or stroke, coronary revascularization, or unstable angina resulting in hospitalization. Secondary endpoints consisted of the composite of CV death as well as non-fatal MI or stroke. Individual endpoints were CV death, MI, stroke, coronary revascularization, and unstable angina requiring hospitalization. This *post hoc* analysis examined hazard ratios (HRs) and 95% confidence intervals (CIs) in patients stratified by history of cigarette smoking, defined as current (within the past 30 days), former, and never smokers.

Statistical analysis

Demographic and baseline characteristics were compared between treatment groups by smoking status using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Time to first occurrences of the primary and key secondary composite endpoints was analysed using a Kaplan–Meier analysis stratified by cardiovascular risk category (pre-existing CVD or diabetes mellitus with one or more CVD risk factors) and baseline ezetimibe use. Hazard ratios and 95% CIs were generated from a corresponding stratified Cox proportional-hazards regression model. Total (first and subsequent) events were analysed using a negative binomial regression model as previously conducted.[10] Additionally, the Li and Lagakos-modified Wei–Lin–Weissfeld method was used to calculate HR and 95% CIs for time to the first, second, or third events, and the negative binomial model was used for the fourth or subsequent events

Table 2 Baseline characteristics of current smokers assigned to IPE or placebo in REDUCE-IT

	Icosapent ethyl (*N* = 628)	Placebo (*N* = 613)
Age (year)		
Median (Q1–Q3)	59.0 (54.0–65.0)	60.0 (54.0–66.0)
≥65 years	182 (29.0)	188 (30.7)
Sex		
Male	481 (76.6)	479 (78.1)
Female	147 (23.4)	134 (21.9)
Race		
White	567 (90.3)	562 (91.7)
Black	10 (1.6)	12 (2.0)
Asian	30 (4.8)	19 (3.1)
Geographic region		
Westernized	443 (70.5)	440 (71.8)
Eastern Europe	174 (27.7)	166 (27.1)
Asia Pacific	11 (1.8)	7 (1.1)
BMI (kg/m^2)		
Median (Q1–Q3)	30.4 (27.4–34.2)	30.1 (26.9–33.3)
BMI ≥30 kg/m^2	340 (54.1)	310 (50.6)
CV risk category		
Secondary prevention	487 (77.5)	469 (76.5)
Primary prevention	141 (22.5)	144 (23.5)
Diabetes		
Type 1	6 (1.0)	10 (1.6)
Type II	323 (51.4)	325 (53.0)
hs-CRP (mg/L)	2.9 (1.5–5.7)	2.6 (1.3–5.8)
Triglycerides (mg/dL)	228.0 (184.0–289.5)	221.5 (179.0–278.0)
HDL-C (mg/dL)	38.0 (33.0–44.0)	38.5 (33.5–44.5)
LDL-C (mg/dL)	[a]76.0 (63.0–91.0)	80.0 (66.0–92.0)
EPA (μg/mL)	25.4 (16.6–37.7)	24.8 (16.0–38.2)

Values are *n* (%) or median (Q1–Q3), unless otherwise indicated. Age (year) is at randomization.
[a]Significant between-group differences ($P < 0.05$). BMI = body mass index.

Table 3 Baseline medications of current smokers in REDUCE-IT

Medication at baseline	Icosapent ethyl (*N* = 628)	Placebo *N* = (613)
Antidiabetes	291 (46.3)	307 (50.1)
Antihypertensive	588 (93.6)	567 (92.5)
Antiplatelet	507 (80.7)	500 (81.6)
1 antiplatelet	350 (55.7)	361 (58.9)
≥2 antiplatelets	157 (25.0)	139 (22.7)
Anticoagulant	50 (8.0)	50 (8.2)
Anticoagulant + antiplatelet	15 (2.4)	19 (3.1)
ACE inhibitor or ARB	461 (73.4)	458 (74.7)
ACE	332 (52.9)	345 (56.3)
ARB	136 (21.7)	120 (19.6)
Beta-blocker	454 (72.3)	442 (72.1)
Statin	627 (99.8)	609 (99.3)
Statin intensity		
Low	34 (5.4)	39 (6.4)
Moderate	397 (63.2)	379 (61.8)
High	196 (31.2)	191 (31.2)
Ezetimibe use	36 (5.7)	34 (5.5)

Values are *n* (%). There were no significant between-group differences in baseline characteristics in current smokers assigned to IPE or placebo.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

as a supportive analysis. *P*-values presented are nominal and exploratory with no adjustment for multiple comparisons. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Study population and baseline characteristics

Smoking status was available in 8177 of the 8179 study subjects and consisted of current smokers ($n = 1241$), former smokers ($n = 3672$), and never smokers ($n = 3264$).

Selected baseline characteristics of current, former, and never smokers are shown in *Table 1*. Compared with never smokers, current smokers were younger, less likely to be obese or have Type II diabetes or renal insufficiency, but were more likely to have pre-existing CVD, elevated hs-CRP, and dyslipidaemia (*P*-value < 0.0001 for all).

Current cigarette smokers assigned to IPE had lower levels of LDL-C at baseline (median, 76 vs. 80 mg/dL; $P = 0.02$), but there were no statistically significant differences in median TG, HDL-C, hs-CRP, or EPA levels at baseline (*Table 2*). Likewise, there were no differences in cardiac medication use in current smokers assigned to IPE or placebo, with high rates of antihypertensives, antiplatelets, and statin use at baseline in both groups (*Table 3*).

Clinical outcomes

The median follow-up time was 4.9 years. In patients classified as current smokers and compared with placebo, IPE significantly decreased the incidence of the primary composite endpoint from 24.5 to 19.7% (HR: 0.79; 95% CI: 0.62–1.00; $P = 0.05$) with an absolute risk reduction (ARR) of 4.7 and number needed to treat (NNT) of 21 to prevent 1 major CVD event over a median 5.8 year period as well as in total events (rate ratio: 0.74: 95% CI: 0.55–0.99; $P = 0.04$). When combining current and former smokers ($n = 4913$), IPE use was associated with significant reductions in time to the primary composite endpoint (HR: 0.77; 95% CI: 0.68–0.87; $P < 0.0001$) with an ARR of 4.9 (95% CI: 2.6, 7.2) and NNT of 20 and in total events (rate ratio: 0.71: 95% CI: 0.61–0.82; $P < 0.0001$) (*Figure 1*). Compared with placebo, IPE use in current/former smokers was also associated with reductions in the key secondary composite endpoint from 15.3 to 12.0% (HR: 0.77; 95% CI: 0.66–0.89; $P = 0.0006$) and in total events (RR: 0.74; 95% CI: 0.62–0.88; $P = 0.0006$) (*Figures 2* and *3*).

In addition to reductions in the primary and key secondary composite endpoints, other endpoints identified IPE treatment in current/former smokers to be associated with 23% relative risk reduction (RRR) in CV death or non-fatal MI ($P = 0.002$), 30% RRR in fatal or non-fatal MI ($P = 0.0004$), 26% RRR in urgent or emergent revascularization ($P = 0.004$), and 19% RRR in the composite of total mortality, non-fatal MI, and non-fatal stroke ($P = 0.004$), with an ARR of 2.8% (CV death or non-fatal MI), 2.8% (fatal or non-fatal MI), 2.1% (urgent or emergent revascularization), and 3% (total mortality, non-fatal MI, and non-fatal stroke), (*Figure 3*). Never smokers also derived benefit from IPE with a 28% RRR in the primary composite

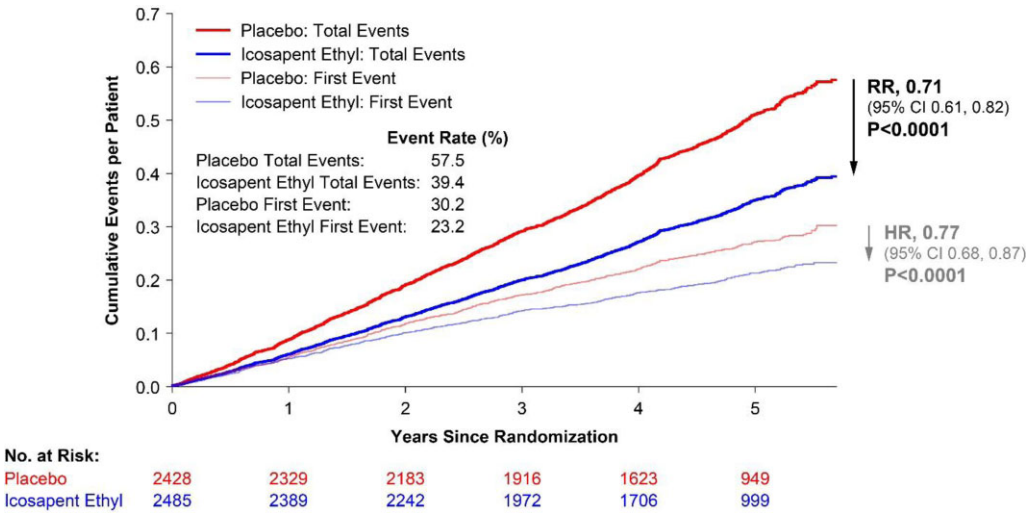

Figure 1 Time to first and total (first and subsequent) primary composite endpoint among current/former smokers.

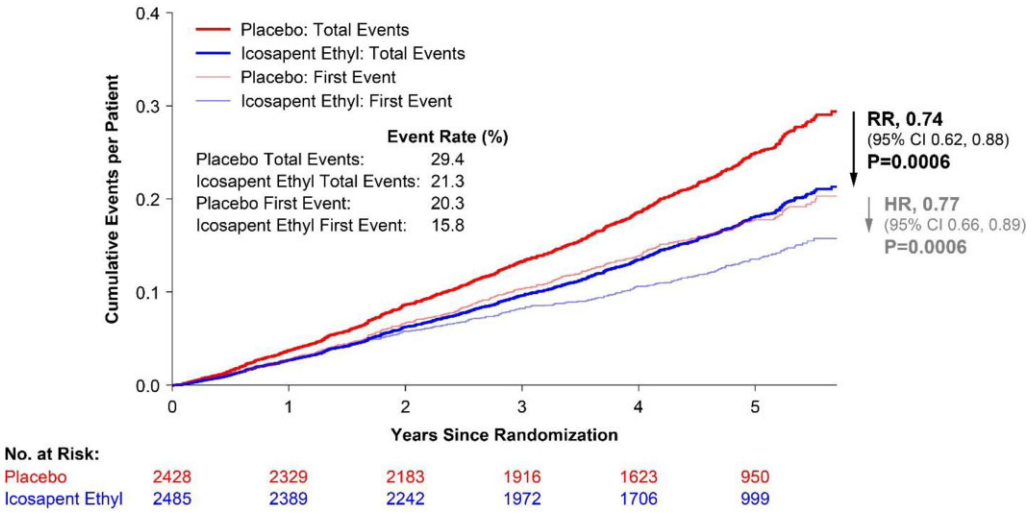

Figure 2 Time to first and total (first and subsequent) key secondary composite endpoint among current/former smokers.

endpoint (95% CI: 0.61–0.85; $P < 0.0001$) and a 35% reduction in total events (95% CI: 0.53–0.80; $P < 0.0001$) (*Figure 4*). When stratified by smoking status, IPE was generally associated with significant reductions in efficacy endpoints for current, former, and never smokers (*Figure 5*). Overall, similar rates in the primary efficacy endpoint were observed in IPE-treated current smokers (23.8%) and former smokers (23.0%) as in placebo-treated never smokers (25.7%) (*Figure 6*).

Hospitalization for positively adjudicated atrial fibrillation or flutter was higher in combined current/former smokers receiving IPE than those receiving placebo (3.3 vs. 2.2%; log-rank $P = 0.01$) with a similar pattern in current smokers (2.7 vs. 1.5%; log-rank $P = 0.12$). Similarly, higher treatment-emergent bleeding adverse events occurred in current/former smokers (13.4 vs. 11.4%; Fisher's exact $P = 0.03$) with a similar pattern in current smokers only (10.7 vs. 9.8%; Fisher's exact $P = 0.64$); there was no significant difference in haemorrhagic stroke in current/former smokers (0.4 vs. 0.2%; Fisher's exact $P = 0.12$) or in current smokers (0.2 vs. 0.2%; Fisher's exact $P = 1.0$).

Discussion

In this analysis from REDUCE-IT, the benefit of IPE was essentially consistent across subgroups defined according to smoking history. While the current smokers were more likely to have an activated inflammatory status compared with former smokers [median baseline hs-CRP 2.7 vs. 2.1 mg/L ($P < 0.0001$)], former smokers were more likely to be 65 years or older [51.3 vs. 29.8% ($P < 0.0001$)], with associated co-morbidities that included obesity [59.4 vs. 52.4% ($P < 0.0001$)], and renal insufficiency or stage 3 chronic kidney disease [10.5 vs. 7.8% ($P = 0.006$)] (Supplementary material online, *Table S1*) that may have contributed to a higher level of oxidative stress in this

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
Primary Composite Endpoint	465/2485 (18.7)	573/2428 (23.6)	0.77 (0.68, 0.87)	<0.0001
Key Secondary Composite Endpoint	297/2485 (12.0)	371/2428 (15.3)	0.77 (0.66, 0.89)	0.0006
Cardiovascular Death or Nonfatal Myocardial Infarction	253/2485 (10.2)	316/2428 (13.0)	0.77 (0.65, 0.90)	0.002
Fatal or Nonfatal Myocardial Infarction	169/2485 (6.8)	233/2428 (9.6)	0.70 (0.57, 0.85)	0.0004
Urgent or Emergent Revascularization	160/2485 (6.4)	208/2428 (8.6)	0.74 (0.60, 0.91)	0.004
Cardiovascular Death	103/2485 (4.1)	122/2428 (5.0)	0.81 (0.62, 1.05)	0.12
Hospitalization for Unstable Angina	80/2485 (3.2)	105/2428 (4.3)	0.74 (0.56, 0.99)	0.04
Fatal or Nonfatal Stroke	64/2485 (2.6)	75/2428 (3.1)	0.83 (0.59, 1.16)	0.27
Total Mortality / Nonfatal Myocardial Infarction / Nonfatal Stroke	366/2485 (14.7)	430/2428 (17.7)	0.81 (0.71, 0.93)	0.004
Total Mortality	180/2485 (7.2)	190/2428 (7.8)	0.91 (0.74, 1.12)	0.38

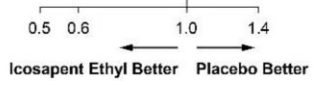

Figure 3 Forest plot of efficacy endpoints among current/former smokers.

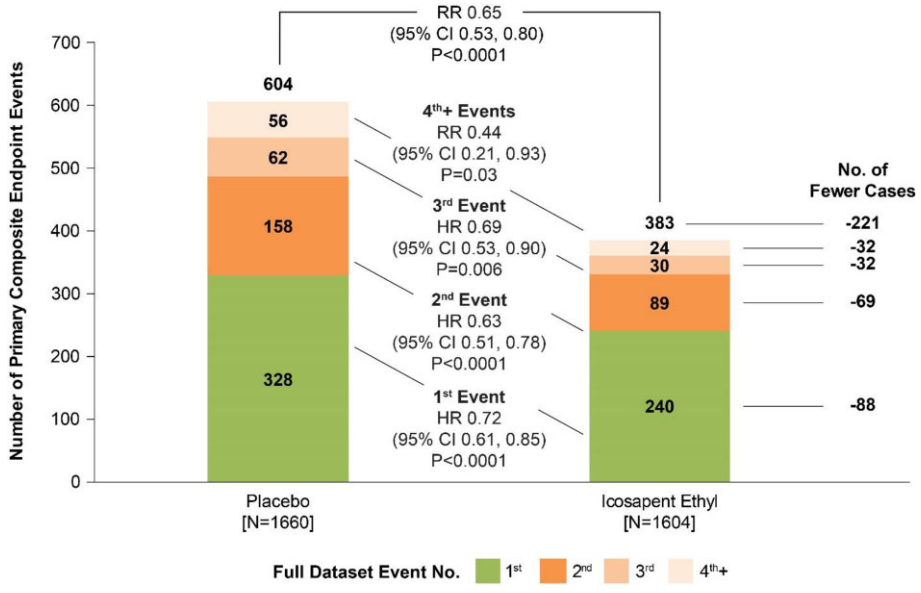

Figure 4 Total (first and subsequent) events for the primary composite endpoint among never smokers.

subgroup.[11,12] Thus, both subgroups (current and former smokers) were at increased atherothrombotic risk at baseline and both benefitted to a similar degree with respect to the primary endpoint following IPE administration. Similarly, IPE reduced the risk of CVD in smokers to that of never smokers on placebo. These novel findings were observed despite the use of effective therapies (e.g. antiplatelets, statins) in a cohort at especially high risk of incident and recurrent CVD.[13,14] Smoking as little as one cigarette daily raises the risk of CVD 40–50% with continued smoking associated with elevated likelihood of fatal or recurrent non-fatal events.[15,16] Yet, despite the overall decline in smoking prevalence worldwide, rates remain sufficiently elevated[17] with recent concerns focused on CV-related complications, including heart failure, arrhythmias, and venous thromboembolism.[18–21] Consequently, every effort should be made to reinforce smoking cessation efforts in cigarette users because the risk of recurrent CVD events adjusts downward to levels observed in a never smoker within 3 years, while CVD mortality is reduced by 50% within 5 years.[22]

Endpoint / Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value	Int. P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Composite Endpoint	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	<0.0001	
Smoking Status					0.79
Current	124/628 (19.7)	150/613 (24.5)	0.79 (0.62, 1.00)	0.05	
Former	341/1857 (18.4)	423/1815 (23.3)	0.76 (0.66, 0.88)	0.0002	
Never	240/1604 (15.0)	328/1660 (19.8)	0.72 (0.61, 0.85)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	<0.0001	
Smoking Status					0.65
Current	85/628 (13.5)	110/613 (17.9)	0.74 (0.56, 0.99)	0.04	
Former	212/1857 (11.4)	261/1815 (14.4)	0.77 (0.64, 0.92)	0.005	
Never	162/1604 (10.1)	235/1660 (14.2)	0.69 (0.56, 0.84)	0.0002	
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6)	507/4090 (12.4)	0.75 (0.66, 0.86)	<0.0001	
Smoking Status					0.85
Current	72/628 (11.5)	95/613 (15.5)	0.73 (0.54, 0.99)	0.04	
Former	181/1857 (9.7)	221/1815 (12.2)	0.78 (0.64, 0.95)	0.01	
Never	139/1604 (8.7)	191/1660 (11.5)	0.73 (0.59, 0.91)	0.004	
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1)	355/4090 (8.7)	0.69 (0.58, 0.81)	<0.0001	
Smoking Status					0.61
Current	43/628 (6.8)	69/613 (11.3)	0.60 (0.41, 0.88)	0.009	
Former	126/1857 (6.8)	164/1815 (9.0)	0.74 (0.59, 0.93)	0.01	
Never	81/1604 (5.0)	122/1660 (7.3)	0.67 (0.50, 0.88)	0.005	
Urgent or Emergent Revascularization	216/4089 (5.3)	321/4090 (7.8)	0.65 (0.55, 0.78)	<0.0001	
Smoking Status					0.09
Current	41/628 (6.5)	57/613 (9.3)	0.70 (0.47, 1.05)	0.08	
Former	119/1857 (6.4)	151/1815 (8.3)	0.76 (0.60, 0.96)	0.02	
Never	56/1604 (3.5)	113/1660 (6.8)	0.49 (0.36, 0.67)	<0.0001	
Cardiovascular Death	174/4089 (4.3)	213/4090 (5.2)	0.80 (0.66, 0.98)	0.03	
Smoking Status					0.87
Current	35/628 (5.6)	38/613 (6.2)	0.90 (0.57, 1.42)	0.65	
Former	68/1857 (3.7)	84/1815 (4.6)	0.77 (0.56, 1.06)	0.10	
Never	71/1604 (4.4)	91/1660 (5.5)	0.79 (0.58, 1.07)	0.13	
Hospitalization for Unstable Angina	108/4089 (2.6)	157/4090 (3.8)	0.68 (0.53, 0.87)	0.002	
Smoking Status					0.44
Current	20/628 (3.2)	22/613 (3.6)	0.89 (0.49, 1.63)	0.71	
Former	60/1857 (3.2)	83/1815 (4.6)	0.70 (0.51, 0.98)	0.04	
Never	28/1604 (1.7)	52/1660 (3.1)	0.55 (0.35, 0.87)	0.009	
Fatal or Nonfatal Stroke	98/4089 (2.4)	134/4090 (3.3)	0.72 (0.55, 0.93)	0.01	
Smoking Status					0.43
Current	18/628 (2.9)	21/613 (3.4)	0.84 (0.45, 1.57)	0.58	
Former	46/1857 (2.5)	54/1815 (3.0)	0.82 (0.55, 1.21)	0.31	
Never	34/1604 (2.1)	59/1660 (3.6)	0.58 (0.38, 0.88)	0.010	
Total Mortality / Nonfatal Myocardial Infarction / Nonfatal Stroke	549/4089 (13.4)	690/4090 (16.9)	0.77 (0.69, 0.86)	<0.0001	
Smoking Status					0.41
Current	100/628 (15.9)	123/613 (20.1)	0.78 (0.60, 1.02)	0.07	
Former	266/1857 (14.3)	307/1815 (16.9)	0.82 (0.70, 0.97)	0.02	
Never	183/1604 (11.4)	260/1660 (15.7)	0.70 (0.58, 0.85)	0.0002	
Total Mortality	274/4089 (6.7)	310/4090 (7.6)	0.87 (0.74, 1.02)	0.09	
Smoking Status					0.62
Current	53/628 (8.4)	52/613 (8.5)	1.00 (0.68, 1.47)	0.99	
Former	127/1857 (6.8)	138/1815 (7.6)	0.88 (0.69, 1.12)	0.31	
Never	94/1604 (5.9)	120/1660 (7.2)	0.79 (0.60, 1.04)	0.09	

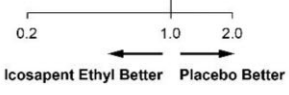

Figure 5 Forest plot of selected efficacy endpoints stratified by smoking status.

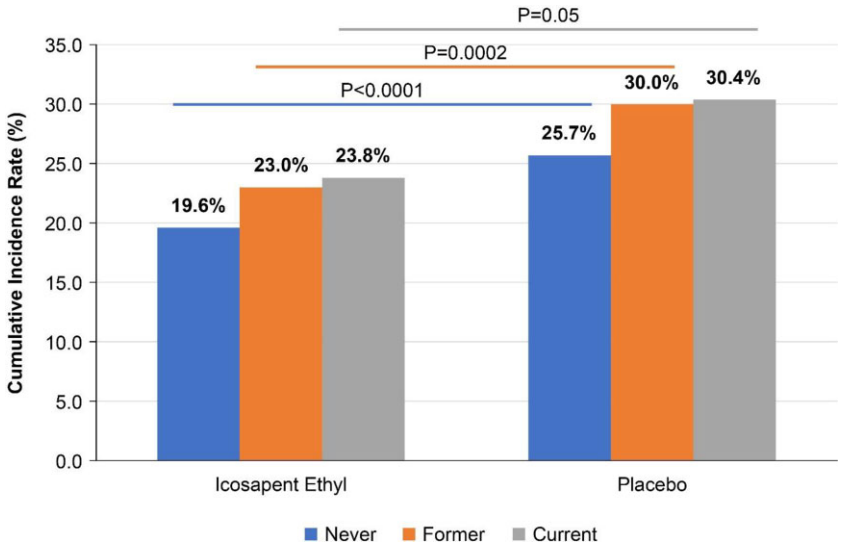

Figure 6 Effect of icosapent ethyl vs. placebo on the primary composite endpoint in never ($N = 3264$), former ($N = 3672$), and current ($N = 1241$) smokers. Cumulative incidence rates are estimated by 5.7 years from the Kaplan–Meier model.

There are several reasons supporting IPE in providing non-specific benefits to cigarette smokers at increased CVD risk. Mechanistically, IPE neutralizes many of the pro-atherothrombotic and incendiary effects of smoking, namely inflammation, oxidative stress, endothelial dysfunction, and platelet hyperreactivity.[23,24]

In the current study, hs-CRP was reduced in IPE-treated current/former smokers, albeit to a similar extent compared with never smokers (Supplementary material online, *Table S2*).

Secondly, the combination of HTG and diabetes, the primary metabolic phenotype in the current study, is at elevated risk of non-alcoholic fatty liver disease[25] and chronic kidney disease, both independent predictors of CVD, with the latter recently shown to be associated with better CVD outcomes following IPE treatment.[26] Finally, *in vitro* studies have demonstrated that EPA improves nitric oxide availability following exposure to modified (oxidized) LDL with a preferential benefit of EPA on endothelial cell function.[27] The associated improvement in the EPA/arachidonic acid (AA) ratio, a predictor of CVD risk,[28] may in turn blunt the higher pro-inflammatory AA levels and reduced EPA/AA ratio induced by cigarette smoking.[29] Taken together, the current study raises the possibility that IPE may limit CV-based deleterious effects of cigarette smoking, thereby adding to the growing list of CVD-related benefits attributable to this compound.[30–35]

Limitations of the study

The data contained herein were derived from *post hoc* analyses that are hypothesis generating. As such, one cannot determine the extent to which other therapies may have impacted the results as the use of these therapies was not balanced at baseline, as would ordinarily have been the case in a randomized controlled study. Interestingly, however, there was greater use of antiplatelet therapies at baseline in current and former smokers compared with non-smokers (81.1% and 82.6% vs. 75.1%; $P < 0.0001$), and patients were matched for statin use irrespective of smoking status (>99.5% for each group; *Table 1*).

Another limitation is that the three groups of patients (current smokers, former smokers, and never smokers) were defined as self-reported and the number of cigarettes smoked daily, the number of pack years, or the duration of time that former smokers quit was not collected. Based on the retrospective design of the study, insufficient quantification of smoking status, and other co-morbidities (e.g. CKD, diabetes) linked to elevated CVD risk in REDUCE-IT patients, the benefit of IPE use in current/former smokers can only be viewed as an association.

As such, future studies should be powered accordingly to determine the extent to which IPE may improve CVD outcomes in active cigarette smokers or in patients living in areas of high pollution exposure.

Conclusions

In this analysis of REDUCE-IT, IPE was associated with reduced CVD risk in current and former cigarette smokers to the level observed in the never smoker placebo group. These *post hoc* findings are preliminary and need to be validated prospectively.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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