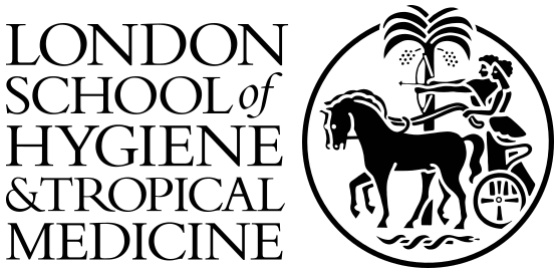

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Letters

Reduction in First and Total Ischemic Events With Icosapent Ethyl Across Baseline Triglyceride Tertiles

Triglyceride elevation has re-emerged as a potent marker of residual cardiovascular risk in statin-treated patients (1). Converging lines of evidence from epidemiological analyses, Mendelian randomization studies, and outcome data from REDUCE-IT (Reduction of Cardiovascular Events with EPA-Intervention Trial) support even moderately elevated triglycerides as being associated with increased cardiovascular risk and as a potential target of therapy (1,2).

REDUCE-IT randomized 8,179 statin-treated patients with triglycerides ≥135 and <500 mg/dl (median baseline of 216 mg/dl); low-density lipoprotein (LDL) cholesterol >40 and ≤100 mg/dl (median baseline of 75 mg/dl); and with a history of atherosclerosis (coronary, cerebral, or peripheral) or with diabetes and other risk factors to icosapent ethyl 4 g/day or placebo (3,4). Patients were followed for a median of 4.9 years. The primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina, was reduced by 25% (hazard ratio: 0.75; 95% confidence interval: 0.68 to 0.83; $p < 0.0001$). In a pre-specified analysis, total primary endpoint events (first and subsequent events) were significantly reduced by 30% (rate ratio: 0.70; 95% CI: 0.62 to 0.78; $p < 0.0001$) (5). Here, we examined by pre-specified baseline triglyceride tertiles the primary endpoint of first event (Cox proportional-hazards model) and total events (negative binomial regression model). REDUCE-IT inclusion criteria specified fasting triglycerides ≥135 and <500 mg/dl at screening, although lower or higher triglycerides were possible at baseline, which was an average of screening and randomization visits. Baseline triglycerides ranged from 81 to 1,401 mg/dl. Median triglycerides across ascending tertiles were 163, 217, and 304 mg/dl. There were large, consistent, statistically significant reductions with icosapent ethyl in the primary endpoint for first (**Figure 1A**) and total events (**Figure 1B**) across all tertiles. Elevated risk occurs at lower triglyceride levels than previously appreciated. While placebo event rates were highest in the upper tertile, where a numerically larger relative risk reduction was suggested, cross-tertile interaction p values were nonsignificant.

To explore this observation further, we considered absolute risk differences, where statistically significant risk reductions with icosapent ethyl across all tertiles and larger reductions in the highest tertile were again observed; but here, unadjusted cross-tertile interaction p values were $p = 0.12$ for first events and $p = 0.03$ for total events. The highest baseline triglyceride tertile likely impacted the interaction p values, with 21.0 ($p < 0.0001$) fewer first events (45.3 vs. 66.3) and 48.3 ($p < 0.0001$) fewer total events (64.4 vs. 107.4) per 1,000 patient-years for icosapent ethyl versus placebo, compared with 11.0 ($p = 0.0055$) (39.6 vs. 50.5) and 10.7 ($p = 0.0168$) (45.9 vs. 56.7) fewer first events, and 21.2 ($p = 0.0028$) (56.4 vs. 74.5) and 21.3 ($p = 0.0113$) (63.2 vs. 86.8) fewer total events in the lowest and middle tertiles, respectively, with icosapent ethyl compared with placebo. In the full cohort, 14.0 first events (43.4 vs. 57.4) and 30.2 total events (61.1 vs. 88.8) were avoided per 1,000 patient-years with icosapent ethyl compared with placebo ($p < 0.0001$ for both).

This suggestion of potential additional benefit in patients with higher triglycerides may be due to a higher baseline risk (triglyceride elevation as a marker of risk) and/or greater icosapent ethyl benefit in patients with higher triglycerides. Further studies are needed to distinguish the contributions of each aspect to the large risk reductions with icosapent ethyl. These REDUCE-IT analyses may help redefine a lower "normal" triglyceride level, analogous to the redefinition of lower normal LDL cholesterol as data emerged supporting therapeutic benefits of LDL lowering with statins, ezetimibe, and PCSK9 inhibitors.

In conclusion, icosapent ethyl 4 g/day significantly reduced first and total ischemic events in

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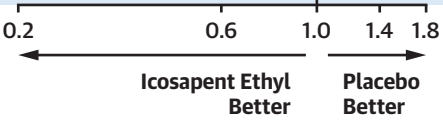
FIGURE 1 Effect of Icosapent Ethyl on First and Total Ischemic Events by Baseline Triglyceride Tertiles

A

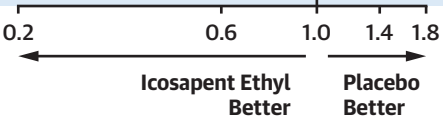
TIME TO FIRST EVENT – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	HR (95% CI)	P-Value
	n/N (%)	n/N (%)		
Primary Composite Endpoint (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	< 0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dl	233/1378 (16.9)	291/1381 (21.1)	0.79 (0.66–0.94)	0.0069
>190 to ≤250 mg/dl	246/1370 (18.0)	283/1326 (21.3)	0.80 (0.68–0.95)	0.0121
>250 to ≤1401 mg/dl	226/1338 (16.9)	327/1382 (23.7)	0.68 (0.57–0.80)	< 0.0001



***P (interaction) = 0.33**

B

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-Value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	< 0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dl	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dl	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dl	64.4	107.4	0.60 (0.50–0.73)	< 0.0001



***P (interaction) = 0.17**

The primary composite endpoint event consists of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. First events **(A)** and subsequent (total) events **(B)** are depicted across tertiles of baseline triglycerides. CI = confidence interval; HR = hazard ratio; ITT = intent to treat; RR = rate ratio.

statin-treated patients with well-controlled LDL cholesterol across a wide range of baseline triglycerides, suggesting that the cardiovascular benefits of icosapent ethyl are tied primarily to baseline risk and non-triglyceride-related effects. Nonetheless, while approximately 10% of REDUCE-IT patients had triglycerides currently considered normal (<150 mg/dl), almost all REDUCE-IT patients had triglycerides greater than what might now be considered an optimal level of <100 mg/dl. Future REDUCE-IT biomarker studies and data analyses will explore the potential mechanisms behind the substantial reductions in cardiovascular risk observed with icosapent ethyl.

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