REDUCE-IT: total ischemic events reduced across the full range of baseline LDL cholesterol and other key subgroups

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Background: REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), a study of 8,179 randomized statin-treated patients with elevated triglycerides (TG) and increased cardiovascular (CV) risk followed for a median of 4.9 years, demonstrated robust results. Icosapent ethyl (IPE), a pure and stable prescription form of eicosapentaenoic acid, 4g/day reduced both time-to-first and total primary endpoint ischemic events (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) by 25% (HR 0.75; 95% CI 0.68–0.83; $p<0.0001$) and 30% (rate ratio 0.70; 95% CI 0.62–0.78; $p<0.0001$), respectively. Similar substantial reductions in first and total key secondary endpoint ischemic events (composite of CV death, nonfatal MI, or nonfatal stroke) were also observed. Demographic and baseline disease characteristics were generally balanced across treatment groups. Time-to-first event analyses showed robust and generally consistent benefit across subgroups. Previous total event analyses by baseline TG demonstrated large, consistent, statistically significant reductions across tertiles, suggesting the CV benefit of IPE is tied primarily to non-TG factors.

Purpose: Further explore the extent to which IPE reduced total primary and key secondary events across prespecified baseline demographic, disease, treatment, and lipid/lipoprotein/inflammatory biomarker subgroups.

Methods: Total events across subgroups were assessed with the prespecified negative binomial regression method. Main outcomes were total (first and subsequent) primary and key secondary composite endpoint events.

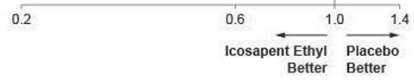
Results: Median baseline LDL-C levels in ascending tertiles were 58, 76, and 96 mg/dL; there were large, significant relative reductions in total primary endpoint events with IPE across tertiles (35%, 28%, and 27%, respectively; interaction p=0.62), with parallel substantial absolute risk reductions. Similar, significant relative reductions of 33%, 28%, and 24% in total key secondary endpoint events were observed, along with substantial absolute risk reductions. Total events analyses of prespecified subgroups also demonstrated robust and generally consistent findings for the primary and key secondary composite endpoints.

Conclusion: REDUCE-IT demonstrated substantial reductions in first and total primary and key secondary endpoint ischemic events, with robust and generally consistent results across baseline TG and LDL-C levels, as well as other prespecified baseline biomarker, demographic, disease, and treatment subgroups. These analyses provide useful insights for clinicians considering the range of patients who may benefit from IPE therapy and suggest that mechanisms beyond the lipid/lipoprotein/inflammatory pathways tested, including mechanisms beyond the LDL receptor pathways, may contribute to the observed substantial reductions in total ischemic burden with IPE therapy.

Figure: Effect of Icosapent Ethyl on Total Ischemic Events by Baseline LDL-C Level

A. Relative Risk Ratio Primary Composite Endpoint

Subgroup	Icosapent Ethyl	Placebo	Rate Ratio (95% CI)	P-value for Interaction
	Rate per 1000 Patient Years			
Baseline LDL Cholesterol (Derived)				0.62
≤67 mg/dl	58.5	92.6	0.65 (0.53–0.79)	
>67-84 mg/dl	62.9	90.7	0.72 (0.59–0.87)	
>84 mg/dl	62.2	83.1	0.73 (0.60–0.89)	



B. Relative Risk Ratio Key Secondary Composite Endpoint

Baseline LDL Cholesterol (Derived)				0.77
≤67 mg/dl	30.4	45.0	0.67 (0.53–0.85)	
>67-84 mg/dl	31.7	45.1	0.72 (0.57–0.90)	
>84 mg/dl	33.1	42.2	0.76 (0.61–0.96)