Icosapent Ethyl Reduces MACE in Patients with Elevated Triglycerides and High or Low Lipoprotein(a) Concentrations: A REDUCE-IT Subanalysis

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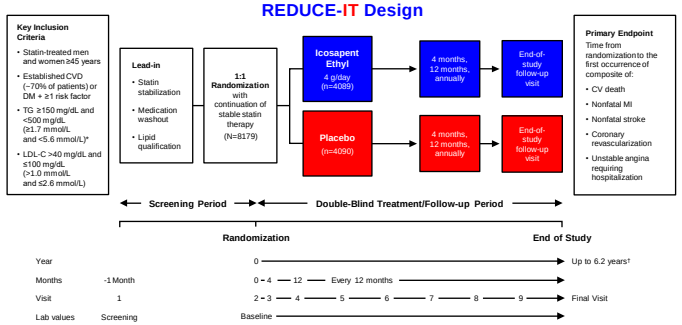
BACKGROUND & DESIGN

REDUCE-IT Design



* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL (≥1.5 mmol/L). Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL (1.7 mmol/L to 2.3 mmol/L), with no variability allowance.

† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

CVD=cardiovascular disease; DM=diabetes mellitus; LDL-C=low density lipoprotein cholesterol; MI=myocardial infarction; TG=triglycerides

Bhatt DL, Steg PG, Brinton EA, et al., on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. ***Clin Cardiol.*** **2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361**

INTRODUCTION

In the full (ITT) REDUCE-IT cohort, icosapent ethyl (IPE) 4 g/day resulted in:[1,2]

- Significant efficacy
  - 25% to 30% reductions in first and total primary and key secondary endpoint events vs. placebo
  - 20% reduction in CV death, 31% in MI, 28% in stroke, 48% in cardiac arrest, 31% in sudden cardiac death
- Low rates of adverse effects, including:
  - Non-statistically significant increase in serious bleeding
  - Increase in the endpoint of atrial fibrillation/flutter (AF/F) requiring ≥24 hours hospitalization (3.1% vs. 2.1%)

Lipoprotein(a) [Lp(a)] concentration is related to CV event risk among those with elevated LDL-C, and few treatments are documented to reduce this residual risk. Whether this relationship holds among those with elevated TGs and well-controlled LDL-C is unknown.

This post hoc analysis of REDUCE-IT explored the CV benefit of IPE across a range of Lp(a) levels.

METHODS

- Participants with available Lp(a) at baseline were included in this analysis; all in this cohort also had LDL-C (measured with preparative ultracentrifugation) and TG assessments at baseline.
- We examined the relationship between continuous baseline Lp(a) mass concentration and risk of MACE (death from CV disease, nonfatal myocardial infarction or stroke, coronary revascularization, or unstable angina) using proportional hazards models with a natural cubic spline of Lp(a) as the predictor variable and adjustment for baseline LDL-C, baseline TG, and treatment assignment. Heterogeneity in the effect of IPE on MACE was assessed by adding a term for the interaction between treatment and the Lp(a) spline to the model.
- We also examined effects of IPE treatment on first MACE among those with Lp(a) ≥50 mg/dL or <50 mg/dL.

RESULTS

- Baseline characteristics of participants included in the analysis cohort were similar between treatment groups (**Table 1**).
- Median baseline Lp(a) concentration was 11.6 mg/dL (Q1, Q3: 5.0, 37.4 mg/dL; **Figure 1B**), and Lp(a) had a significant relationship with MACE across treatment groups (spline P<0.0001; **Figure 1A**).
- The treatment benefit of IPE was consistent across Lp(a) concentrations (interaction P=0.66; **Figure 2**).
- IPE significantly reduced MACE in subgroups ≥50 mg/dL and <50 mg/dL (**Figure 3**). By Kaplan-Meier analyses, MACE absolute risk reduction at 5 years with IPE was 6.5% and 5.7% for those with Lp(a) ≥50 mg/dL and <50 mg/dL, respectively.
- Median absolute change in Lp(a) from baseline to month 12 was 0 (-2.0, 3.3) mg/dL in the IPE group and 0.4 (-1.7, 3.8) mg/dL in the placebo group.

RESULTS (continued)

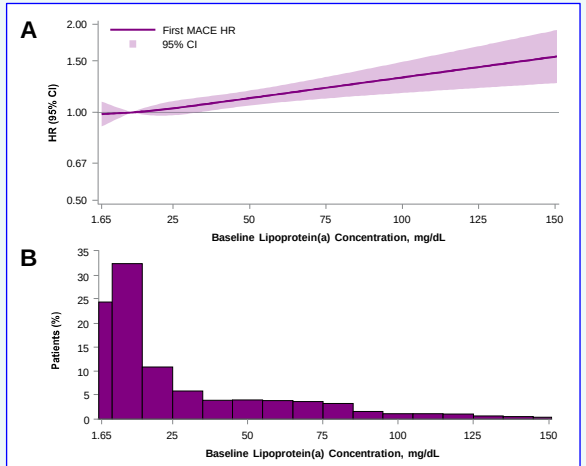
Table 1. Demographic and Baseline Clinical Characteristics of the Analysis Cohort by Treatment Assignment

Characteristic	Icosapent ethyl (n=3515)	Placebo (n=3511)	P-value
Age, y	64 (57, 69)	64 (57, 70)	0.63
Female sex	975 (27.7)	1014 (28.9)	0.30
Geographic region			0.84
United States, Canada, the Netherlands, Australia, New Zealand, and South Africa	2676 (76.1)	2668 (76.0)	
Eastern European	804 (22.9)	803 (22.9)	
Asia-Pacific	35 (1.0)	40 (1.1)	
Cardiovascular risk stratum			0.81
Secondary prevention	2509 (71.4)	2516 (71.7)	
Primary prevention	1006 (28.6)	995 (28.3)	
Ezetimibe use	229 (6.5)	234 (6.7)	0.80
Statin intensity			0.34
Low	230 (6.5)	233 (6.6)	
Moderate	2154 (61.3)	2200 (62.7)	
High	1127 (32.1)	1066 (30.4)	
Unknown	4 (0.1)	12 (0.3)	
Body mass index, kg/m^2	30.9 (27.9, 34.6)	31.0 (28.1, 34.9)	0.23
Systolic blood pressure, mmHg	132 (122, 142)	132 (122, 142)	0.58
Diastolic blood pressure, mmHg	79 (72, 85)	79 (72, 84)	0.57
History of diabetes	2055 (58.5)	2034 (57.9)	0.66
Baseline laboratory data			
Lp(a), mg/dL	11.6 (5.1, 37.9)	11.4 (5.0, 36.8)	0.59
LDL-C, mmol/L	1.91 (1.60, 2.27)	1.97 (1.63, 2.30)	0.0092
LDL-C, mg/dL	74.0 (62.0, 88.0)	76.0 (63.0, 89.0)	
HDL-C, mmol/L	1.03 (0.89, 1.18)	1.03 (0.91, 1.19)	0.12
HDL-C, mg/dL	40.0 (34.5, 45.5)	40.0 (35.0, 46.0)	
Non-HDL-C, mmol/L	3.06 (2.69, 3.43)	3.08 (2.73, 3.46)	0.0299
Non-HDL-C, mg/dL	118.0 (104.0, 132.5)	119.0 (105.5, 133.5)	
ApoB, mg/dL	82.0 (72.0, 93.0)	83.0 (73.0, 93.0)	0.0179
TG, mmol/L	2.46 (2.00, 3.09)	2.46 (2.00, 3.11)	0.91
TG, mg/dL	218.0 (177.5, 274.0)	218.0 (177.0, 275.0)	
HsCRP, mg/L	2.2 (1.1, 4.5)	2.2 (1.1, 4.6)	0.76
Eicosapentaenoic acid, μg/mL	26.1 (17.2, 40.1)	26.1 (17.1, 40.0)	0.98
Arachidonic acid, μg/mL	402.0 (334.0, 481.0)	406.0 (336.0, 484.0)	0.38
Docosahexaenoic acid, μg/mL	66.4 (49.9, 88.9)	65.7 (50.5, 88.4)	0.59
Docosapentaenoic acid, μg/mL	18.6 (14.2, 23.9)	18.3 (14.1, 24.1)	0.49

Values are medians (interquartile range) for continuous variables and n (%) for categorical variables.

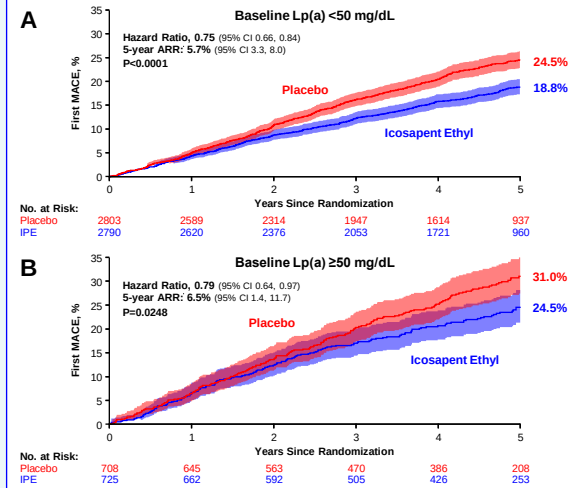
LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; ApoB=Apolipoprotein B; TG=Triglycerides; HsCRP=High sensitivity C-reactive protein.

Figure 1. Spline of First MACE by Baseline Lp(a)



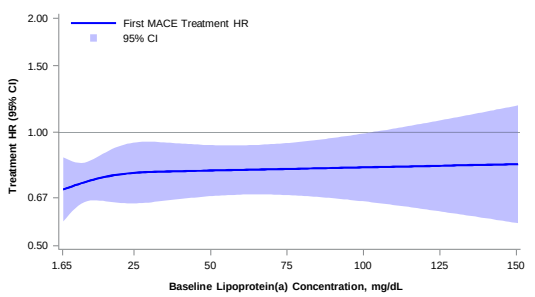
(A) Relative risk, with HR set to 1.00 at the median Lp(a) baseline concentration (11.6 mg/dL). **(B)** Histogram. Figure includes all participants in the analysis cohort (i.e., pooled across treatment groups). Spline is natural cubic with knots specified at the 25th (5.0 mg/dL), 50th (11.6 mg/dL), and 75th (37.4 mg/dL) percentiles of baseline Lp(a) and reflects adjustment for baseline TG, baseline LDL-C, and treatment assignment. X-axis spans from the minimum to the approximate 99th percentile of baseline Lp(a). Spline P<0.0001 adjusted for TG, LDL-C, and treatment assignment; spline P<0.0001 adjusted for TG, LDL-C, treatment assignment, age, sex, race, body mass index, and history of diabetes.

Figure 3. First MACE Kaplan-Meier Estimates by Baseline Lp(a)



(A) Lp(a) concentration <50 mg/dL. **(B)** Lp(a) concentration ≥50 mg/dL. P-values correspond to treatment Hazard Ratios. Shading represents the 95% confidence interval (CI). First MACE incidences for each treatment group and ARRs are based on Kaplan-Meier estimates at 5 years after randomization. Treatment HR × Lp(a) subgroup interaction P=0.68.

Figure 2. Spline of First MACE Treatment HR by Baseline Lp(a)



Spline is natural cubic with knots specified at the 25th (5.0 mg/dL), 50th (11.6 mg/dL), and 75th (37.4 mg/dL) percentiles of baseline Lp(a) and reflects adjustment for baseline TG, baseline LDL-C, treatment assignment, and the interaction between the spline and treatment assignment. The x-axis spans from the minimum to the approximate 99th percentile of baseline Lp(a). Treatment × spline interaction P=0.66.

LIMITATIONS

- 14% of the study population was excluded because of missing baseline Lp(a) assessments.
- Given several differences in baseline characteristics between included and excluded participants, the analysis cohort was a non-random subset of the ITT study population. However, overall relative treatment benefits of IPE on first MACE were similar in the analysis cohort and in the ITT study population; thus it is reasonable to expect that the current findings would apply to the entire study population.
- Although there is growing consensus to measure Lp(a) in molar units, recent findings indicate mass and molar concentrations have similar relationships with CV events at a cohort level, and thus the current findings obtained using a mass concentration would be expected to extend to molar measurement methods.[3]
- REDUCE-IT participants were not selected on the basis of Lp(a) concentration. Therefore, there were relatively fewer patients who had extremely elevated levels that, for example, are being evaluated in studies of Lp(a)-targeting therapies (e.g., ≥70 mg/dL or ≥175 nmol/L).

CONCLUSIONS

- Baseline Lp(a) concentration was prognostic for MACE among patients with elevated TG levels receiving statin therapy.
- Importantly, IPE consistently reduced MACE across a range of Lp(a) levels, including among those with clinically relevant elevations.

DISCLOSURES

REDUCE-IT was sponsored by Amarin Pharma, Inc. This presentation may include off-label and/or investigational uses of drugs.

Dr. Szarek serves as a consultant for Amarin.

Dr. Bhatt served as the principal investigator for REDUCE-IT and his institution received research funding from Amarin.

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