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Letters

Consistency of Benefit of Icosapent Ethyl by Background Statin Type in REDUCE-IT

REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) demonstrated that icosapent ethyl (IPE) 4 g daily resulted in a significant reduction of cardiovascular events in high-risk patients with elevated triglycerides despite low-density lipoprotein cholesterol control with statins (1). The benefits were large and consistent across the range of baseline and achieved triglyceride values (1,2). Thus, although there were beneficial lipid effects, their modest size and limited correlation with outcomes suggested that most of the cardiovascular benefit was attributable to other effects. These include anti-inflammatory, antithrombotic, membrane stabilization, plaque stabilization, cholesterol crystal decreases, and pro-endothelial effects (3). Statins, too, appear to have nonlipid effects that may contribute to their benefit (4) and that may be related to the lipophilicity of a given agent. It remains unclear if the beneficial effects of IPE are modified by statins or if they are independent.

Here, we sought to explore the relevance of the type of background statin treatment on the cardiovascular benefits of IPE. In this exploratory analysis of REDUCE-IT, we examined the primary composite (cardiovascular death, myocardial infarction, stroke, coronary revascularization, or unstable angina) and key secondary composite (cardiovascular death, myocardial infarction, or stroke) endpoints, in a time-to-first-event analysis, in subgroups based on statin agent and lipophilic versus lipophobic statin category.

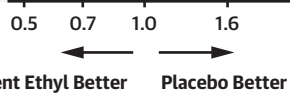
Details regarding trial design, randomization, and patient eligibility have been previously published (1). For the present analyses, background statins were defined as medications taken at any time following randomization, either continuing through the end of the trial or with a stop date after randomization. If a change in statin agent or category occurred after the endpoint, the patient was included in the analysis but with only pre-endpoint statins considered. For statin agent analyses, patients who took >1 statin before the endpoint event were excluded. For lipophilicity analyses, patients on multiple statins were included if all statins were within the same category but were excluded if they spanned both categories before endpoint events. Included agents were atorvastatin, simvastatin, rosuvastatin, and pravastatin, because these represented the majority of statin use. Lipophilic statins included atorvastatin and simvastatin and lipophobic statins included rosuvastatin and pravastatin. The treatment effects within these subgroups were compared to test for an interaction between background statin and IPE efficacy. Heterogeneity of treatment effect was examined by testing the interaction term of treatment by subgroup in the Cox regression model.

A primary endpoint occurred in 17.2% of patients within the IPE group compared with 21.0% in the placebo group among patients on atorvastatin (HR: 0.79; 95% CI: 0.67-0.93; $P = 0.006$), with similar results among other agents (**Figure 1**). Testing the interaction term of treatment by agent yielded an interaction P value of 0.95, indicating no significant difference of IPE efficacy among statin agents. Endpoint rates were 18.1% compared with 22.0% among patients on lipophilic statins (HR: 0.78; 95% CI: 0.69-0.88; $P < 0.0001$) and 15.8% compared with 20.8% among patients on lipophobic statins (HR: 0.75; 95% CI: 0.61-0.93; $P = 0.007$). There was no significant difference in IPE treatment effect among these statin categories (P interaction = 0.67). Similar results were seen with analysis of the key secondary endpoint, with no significant difference of treatment effect among statin agents (P interaction = 0.68) or categories (P interaction = 0.74).

We observed consistent benefits of IPE in the endpoints across background statin agent and category. This key finding offers insight for prescribing physicians that the benefits of IPE are not only additive to those of statin therapy, but also appear not to vary by the particular statin used. This lack of dependence suggests mechanisms that are modified by statin intensity, agent, or lipophilicity are not primary drivers of IPE's clinical efficacy. Further studies may clarify the mechanisms by which IPE reduces cardiovascular risk, including a better understanding of the interplay between other therapies and these mechanisms.

FIGURE 1 Endpoints by Background Statin Agent and Statin Lipophilicity Category

Endpoint/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs Placebo	*P* Value	Interaction *P* Value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Endpoint	705/4,089 (17.2)	901/4,090 (22.0)	0.75 (0.68-0.83)	<0.0001	
Statin Agent					0.95
Atorvastatin	253/1,472 (17.2)	314/1,495 (21.0)	0.79 (0.67-0.93)	0.006	
Simvastatin	188/992 (19.0)	209/918 (22.8)	0.79 (0.65-0.96)	0.02	
Rosuvastatin	110/734 (15.0)	149/741 (20.1)	0.73 (0.57-0.94)	0.01	
Pravastatin	49/266 (18.4)	58/246 (23.6)	0.79 (0.54-1.16)	0.24	
Statin Category					0.67
Lipophilic	475/2,631 (18.1)	581/2,635 (22.0)	0.78 (0.69-0.88)	<0.0001	
Lipophobic	161/1,017 (15.8)	210/1,008 (20.8)	0.75 (0.61-0.93)	0.007	
Key Secondary Endpoint	459/4,089 (11.2)	606/4,090 (14.8)	0.74 (0.65-0.83)	<0.0001	
Statin Agent					0.68
Atorvastatin	168/1,462 (11.5)	225/1,487 (15.1)	0.73 (0.59-0.89)	0.002	
Simvastatin	132/972 (13.6)	134/888 (15.1)	0.86 (0.68-1.10)	0.24	
Rosuvastatin	67/730 (9.2)	94/725 (13.0)	0.71 (0.52-0.97)	0.03	
Pravastatin	35/261 (13.4)	41/238 (17.2)	0.78 (0.50-1.23)	0.29	
Statin Category					0.74
Lipophilic	318/2,618 (12.1)	400/2,618 (15.3)	0.76 (0.66-0.88)	0.0003	
Lipophobic	102/1,008 (10.1)	137/986 (13.9)	0.73 (0.57-0.95)	0.02	



Patients taking >1 statin before the onset of a primary or key secondary endpoint were excluded from statin agent analysis, and patients taking statins with different lipophilicity before the onset of an endpoint were excluded from statin category analysis.

Displayed are the HRs and 95% CIs for the primary composite and key secondary composite endpoints in subgroups according to background statin agent and lipophilicity category. Benefit of icosapent ethyl was consistent across the subgroups. n = number of patients with event; N = total number of patients.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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