Achieved Omega-3 Fatty Acid Levels and Major Adverse Cardiovascular Events

A Secondary Analysis of the STRENGTH Trial

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For the STRENGTH Trial Investigators

Disclosure

Clinical Trials: AbbVie, Amgen, AstraZeneca, Esperion, Eli Lilly, Novartis, Takeda, Resverlogix, Orexigen, Ethicon Endosurgery, Medtronic,The Medicines Company, and Pfizer.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

Background

- Several large clinical trials (ORIGIN n=12536, ASCEND n=15480, VITAL, n=25871) have shown no cardiovascular benefits from supplementation with omega-3 fatty acids.
- Two recent trials, REDUCE-IT (n=8179) and STRENGTH (n=13078) studied higher doses of omega 3 fatty acids, but reported contradictory results:
  - REDUCE-IT reported a HR of 0.75
  - STRENGTH reported a HR of 0.99
- These disparate results have generated considerable controversy with several alternative hypotheses proposed to explain the conflicting results.

Three Hypotheses to Explain Disparate Results

1) The mineral oil placebo used in REDUCE-IT increased LDL-C 10.9% and hsCRP 32.3%, raising concerns whether the favorable results were driven largely by mineral oil toxicity.

   - STRENGTH used corn oil which exhibited neutral effects

2) REDUCE-IT used purified EPA to achieve moderately higher EPA levels compared with STRENGTH. Could higher achieved EPA levels explain the more favorable outcomes?

3) STRENGTH used a mixture of EPA and DHA. Could the DHA component have *exactly* counterbalanced the benefits of EPA, resulting in a precisely neutral outcome in STRENGTH?

The current study designed to examine the 2nd and 3rd hypotheses

STRENGTH Substudy Details

- The STRENGTH study randomized 13,078 patients to omega-3 carboxylic acid (CA) vs. corn oil placebo.
- The primary endpoint was a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization.
- EPA and DHA levels were available in 10,382 patients measured 12 months after randomization.
- The primary outcome measure for this substudy was the HR for the top tertile of achieved EPA and DHA levels in the omega-3 CA group compared with corn oil reference group.

Baseline Characteristics and Medication Use

	Corn Oil	Omega 3 Carboxylic Acid (Tertiles of Achieved EPA)		
		Tertile 1	Tertile 2	Tertile 3
Age (years)	62.5	61.2	62.1	64.2
Female gender	34.9%	36.5%	29.6%	36.6%
Body Mass Index (kg/m^2)	32.5	33.0	33.5	31.1
Established CV disease	54.5%	52.6%	54.2%	54.2%
Diabetes mellitus	70.4%	69.5%	73.4%	67.0%
Hypertension	87.7%	90.0%	89.6%	85.7%
High intensity statin use	52.8%	64.2%	52.6%	41.6%

Median Lipid Measurements after 12 Months

	Corn Oil	Omega 3 Carboxylic Acid (Tertiles of Achieved EPA)		
		Tertile 1	Tertile 2	Tertile 3
LDL-C (mg/dL)	75	76	71	82
HDL-C (mg/dL)	37	37	37	38
Triglycerides (mg/L)	235	198	177	198
Non-HDL-C (mg/dL)	124	119	107	123
Apo B (mg/dL)	56	56	52	57
hsCRP (mg/L)	1.8	1.8	1.8	1.5

Median EPA and DHA Levels after 12 Months

	Corn Oil	Omega 3 Carboxylic Acid (EPA and DHA Tertiles)		
		Tertile 1	Tertile 2	Tertile 3
Plasma EPA (μg/mL)	19	30	90	**151 (443% increase)**
Plasma DHA (μg/mL)	58	67	88	**118 (68% increase)**
RBC EPA (% of total)	0.6%	1.0%	2.9%	4.3%
RBC DHA (% of total)	4.8%	5.7%	6.6%	7.1%

Tertiles of Achieved EPA and Cardiovascular Outcome

Variable		Adjusted HR*	P value
Corn Oil	NA	1.00 (reference)	NA
Achieved plasma EPA levels (µg/mL)	<62.4	0.99	0.95
	62.5-116.3	1.10	0.27
	>116.4	**0.98** (0.83-1.16)	**0.81**

*Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, sex, diabetes, creatinine, non–high-density lipoprotein cholesterol, high sensitivity C-reactive protein, antiplatelets agents, β Blockers, renin angiotensin inhibitors.

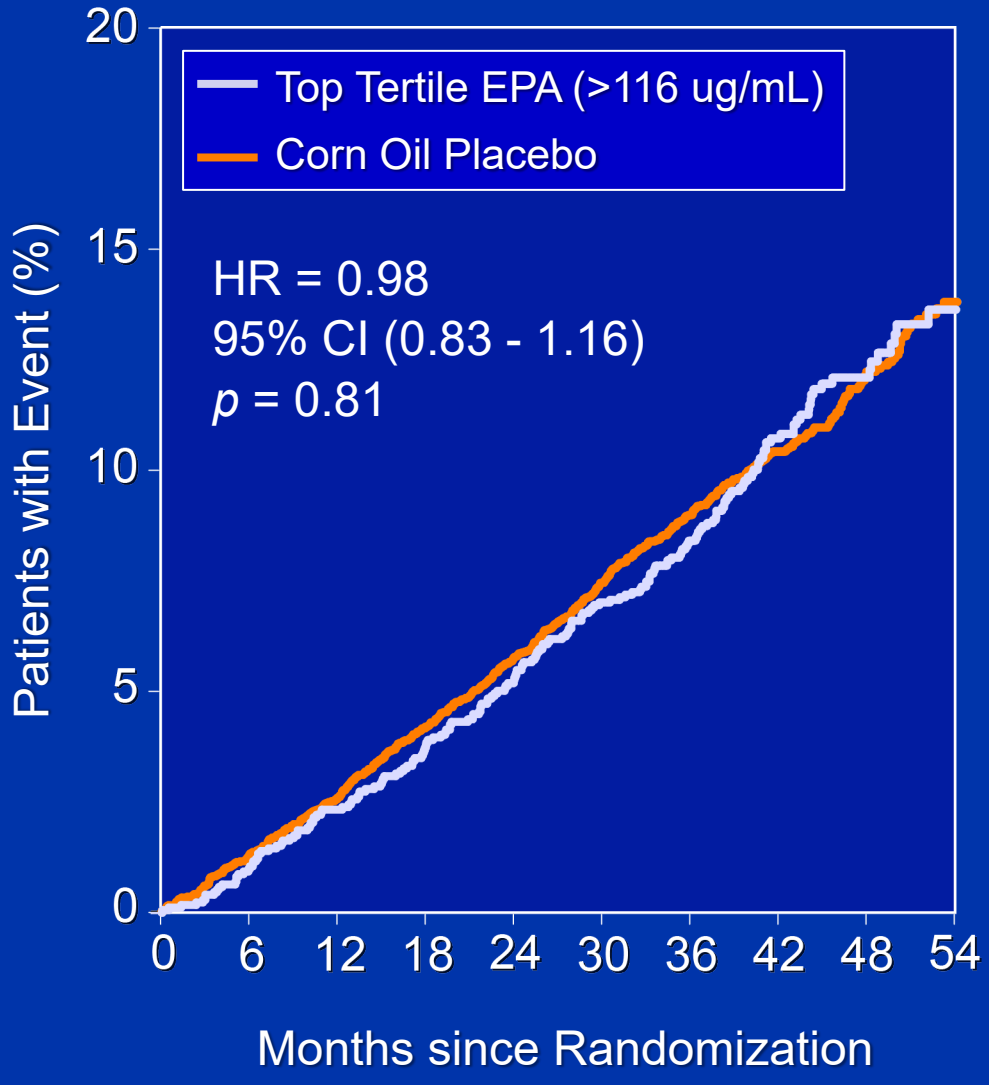
Tertiles of Achieved DHA and Cardiovascular Outcome

Variable		Adjusted HR*	P value
Corn Oil	NA	1.00 (reference)	NA
Achieved plasma DHA levels (µg/mL)	<78.2	1.03	0.74
	78.3-105	1.03	0.74
	>105.2	**1.02** (0.86-1.20)	**0.85**

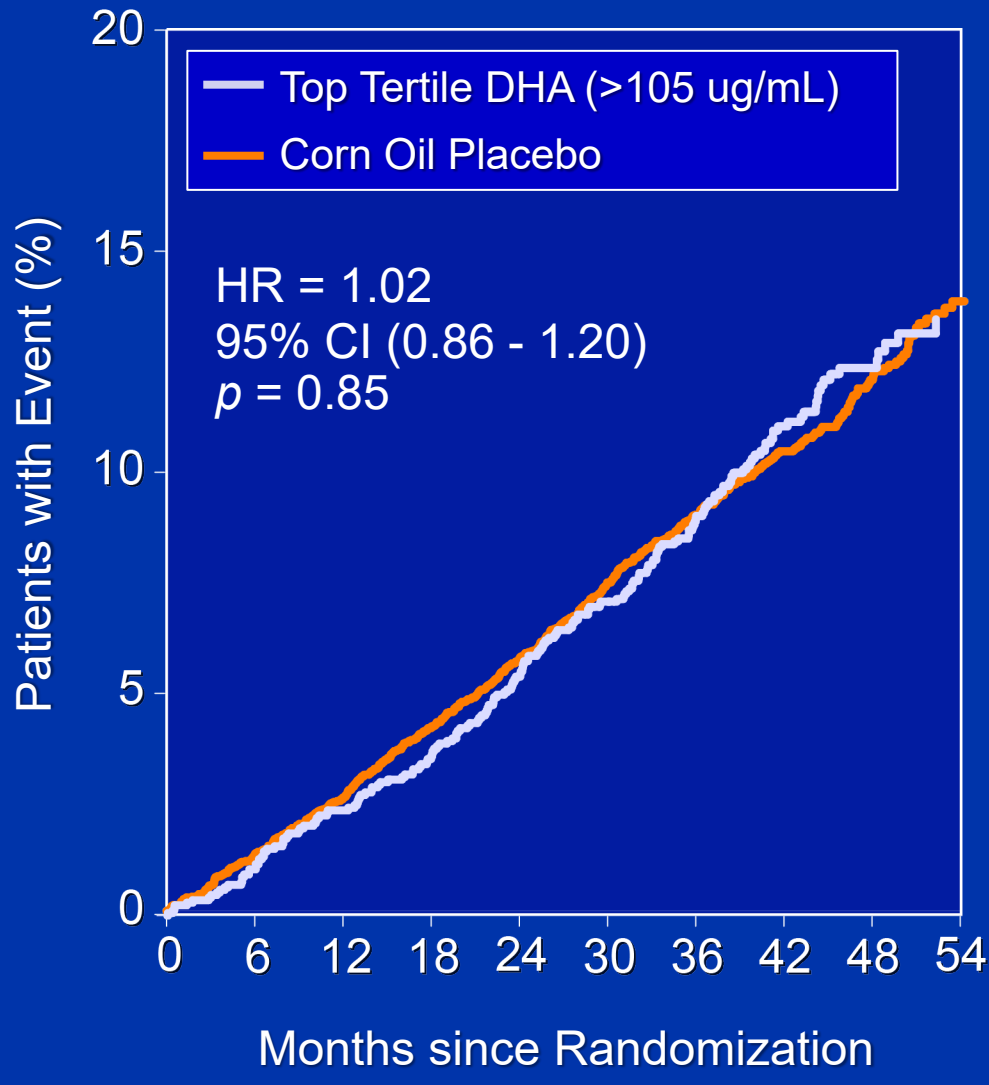
*Adjusted for baseline fatty acid levels, region, cardiovascular disease, age, sex, diabetes, creatinine, non–high-density lipoprotein cholesterol, high sensitivity C-reactive protein, antiplatelets agents, β Blockers, renin angiotensin inhibitors.

MACE: Top Tertile of Achieved EPA and DHA

Plasma EPA vs. Corn Oil

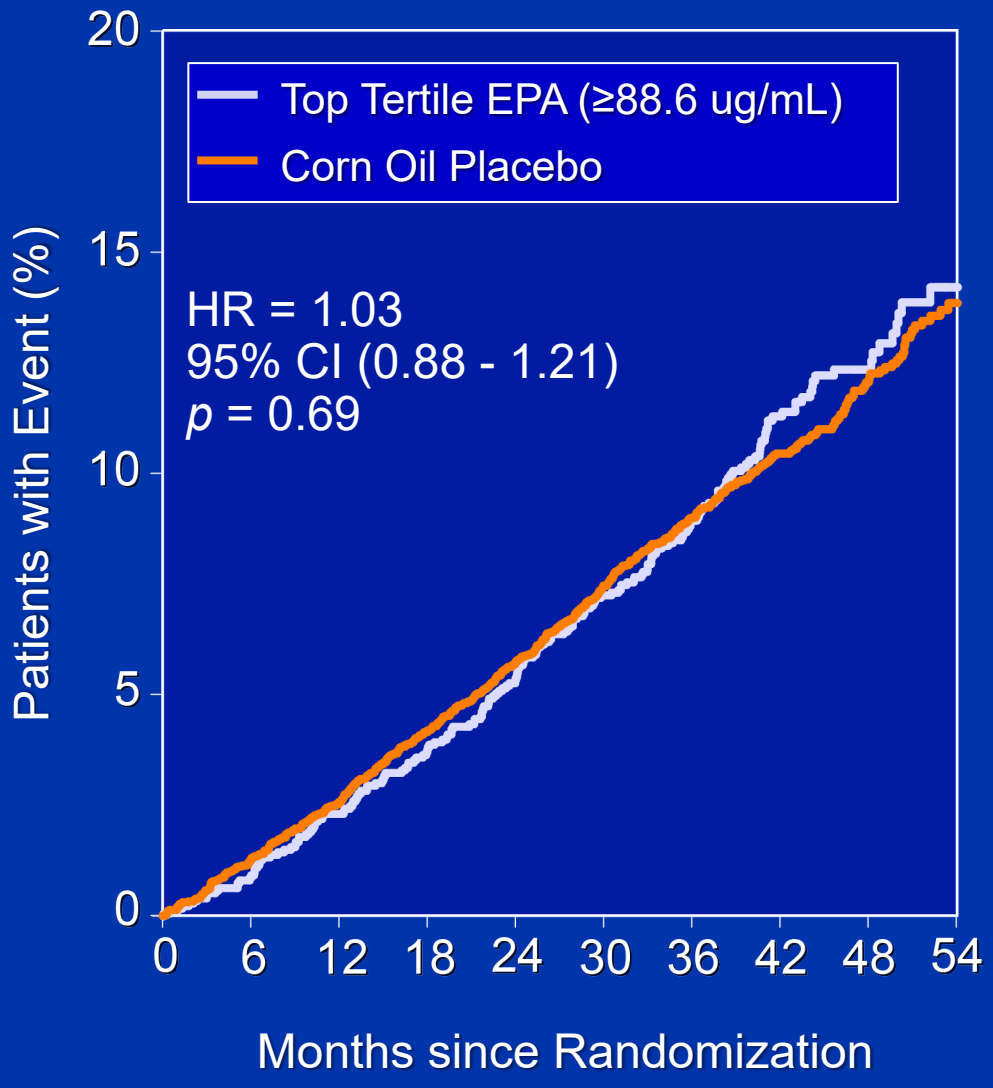


Plasma DHA vs. Corn Oil

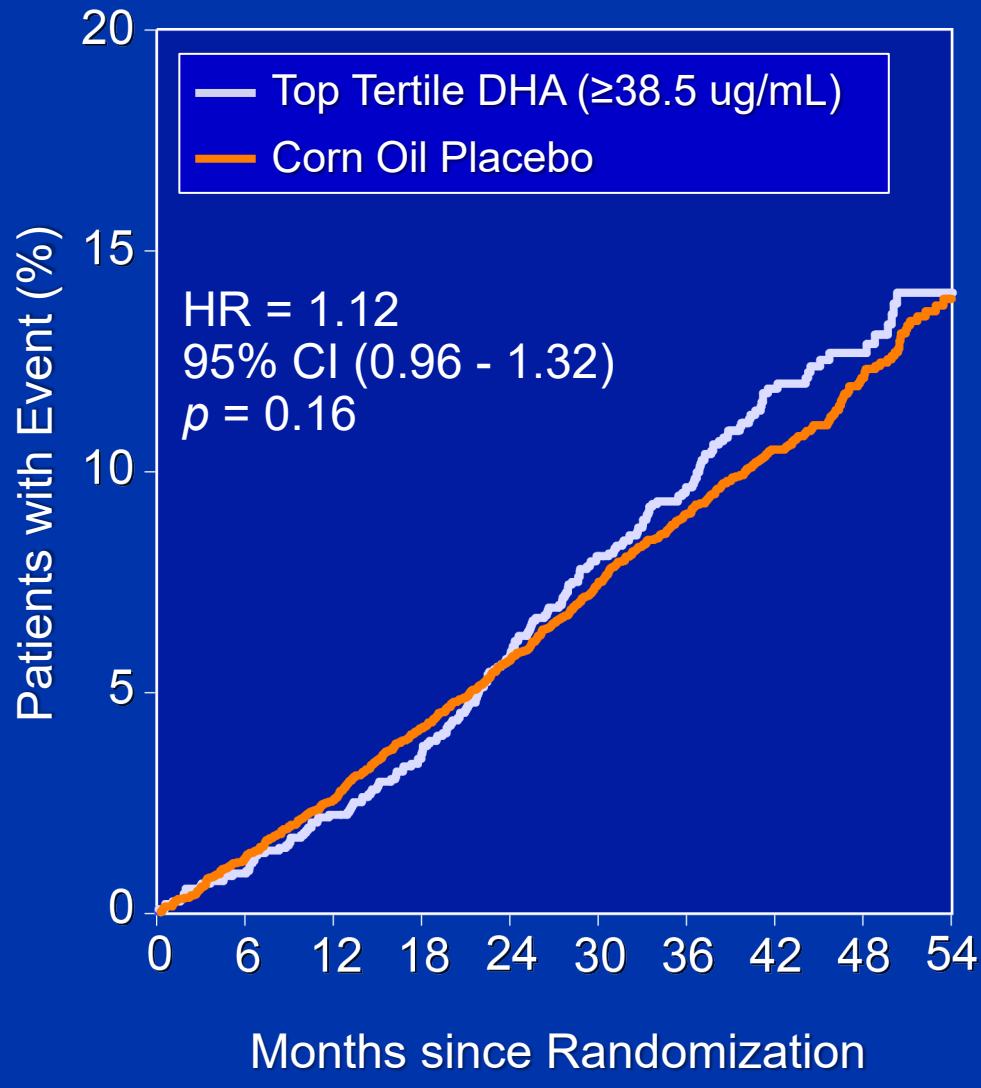


MACE: Top Tertile of Change in EPA and DHA

Change in Plasma EPA

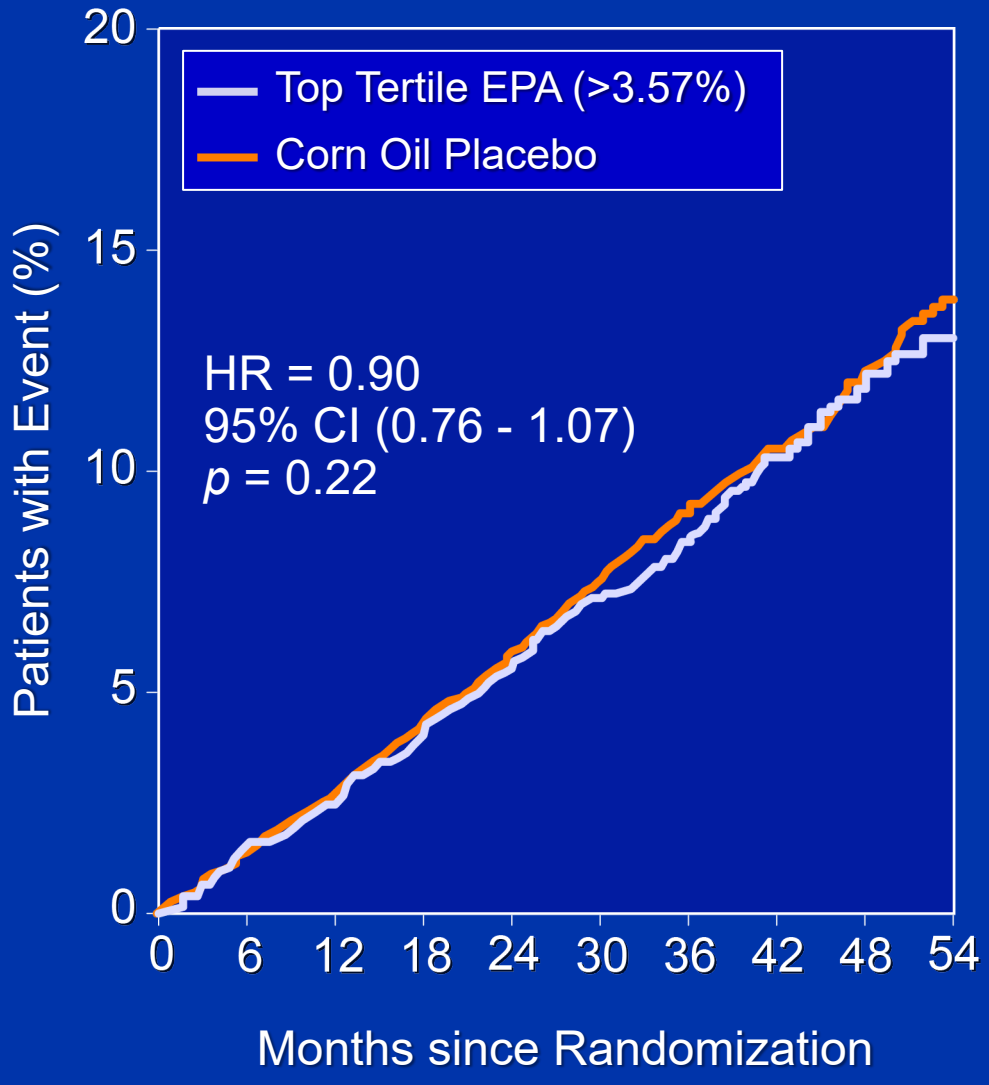


Change in Plasma DHA

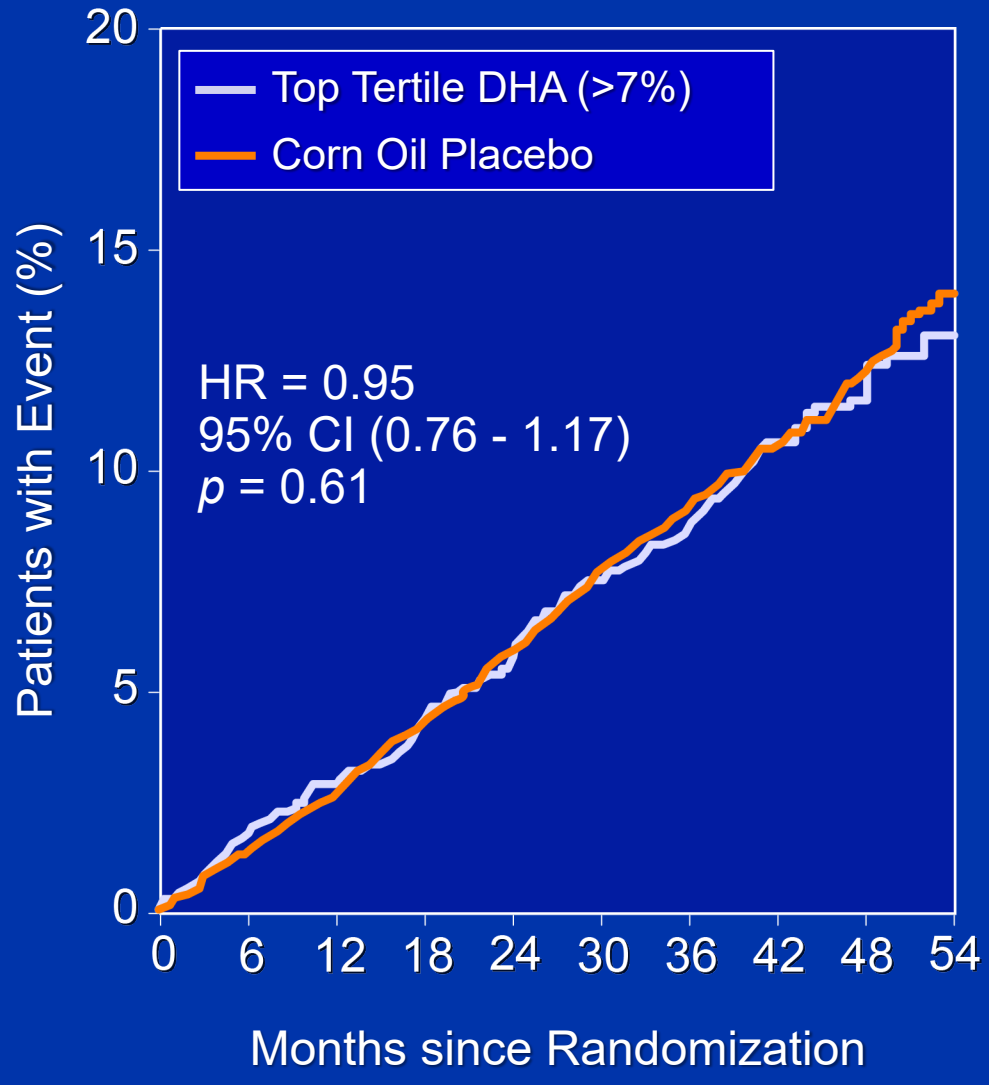


MACE: Top Tertile of Achieved RBC EPA and DHA

RBC EPA vs Corn Oil

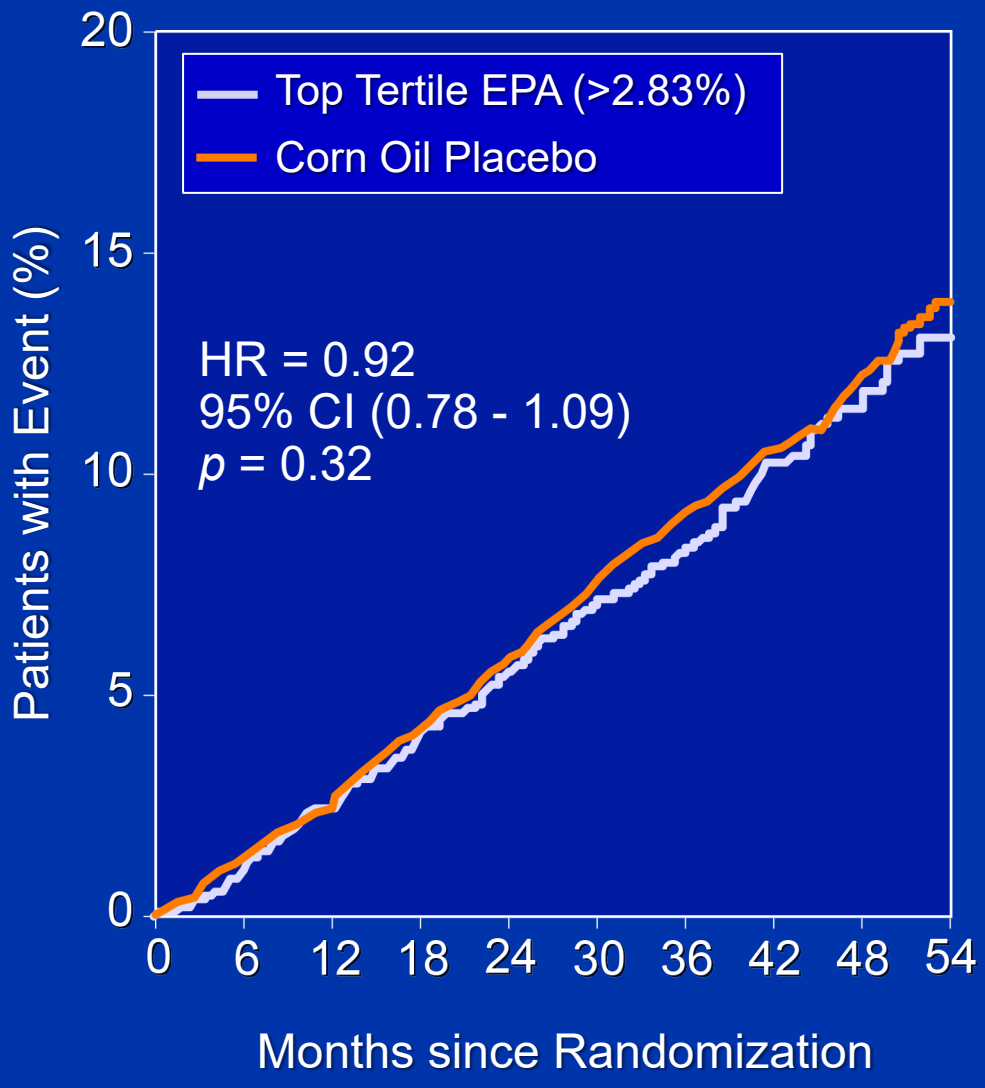


RBC DHA vs Corn Oil

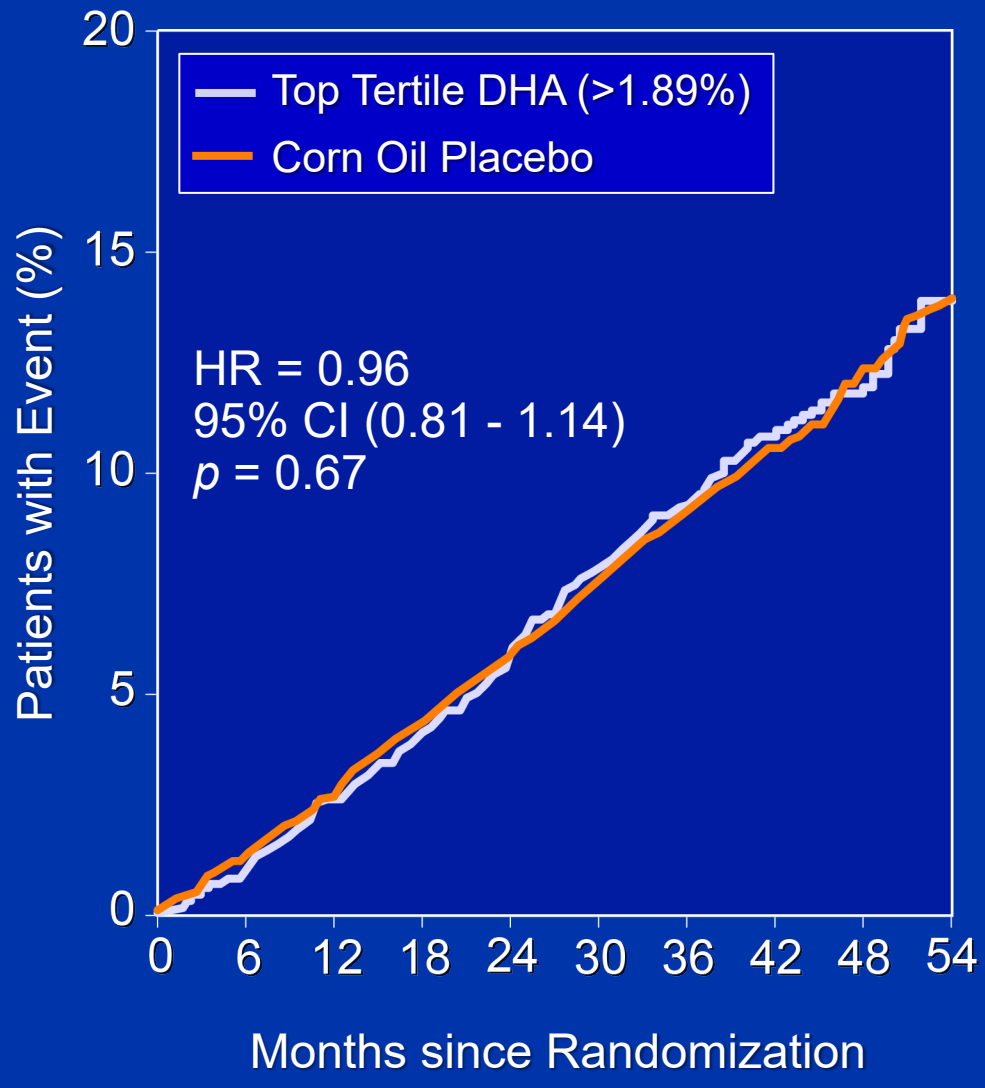


MACE: Top Tertile of Change in RBC EPA and DHA

RBC EPA vs Corn Oil

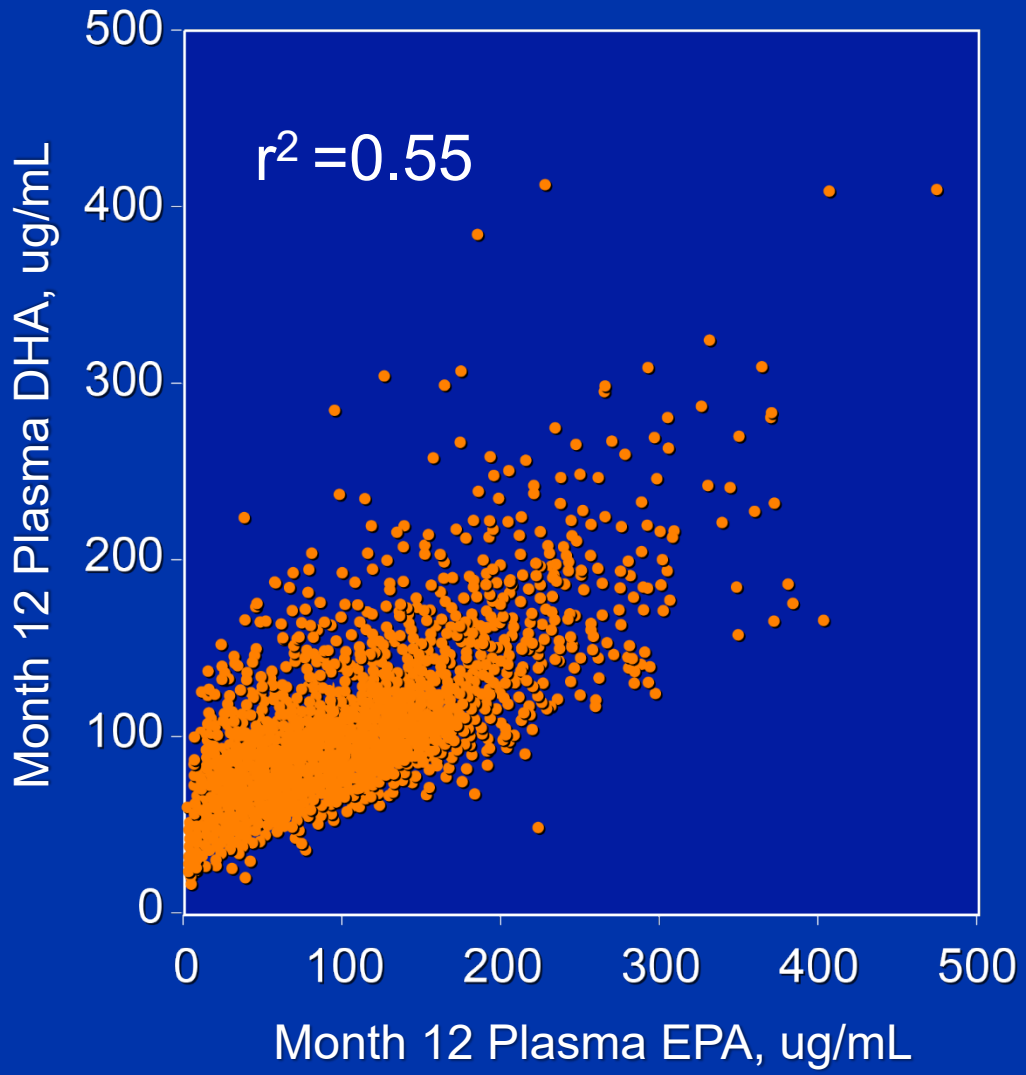


RBC DHA vs Corn Oil

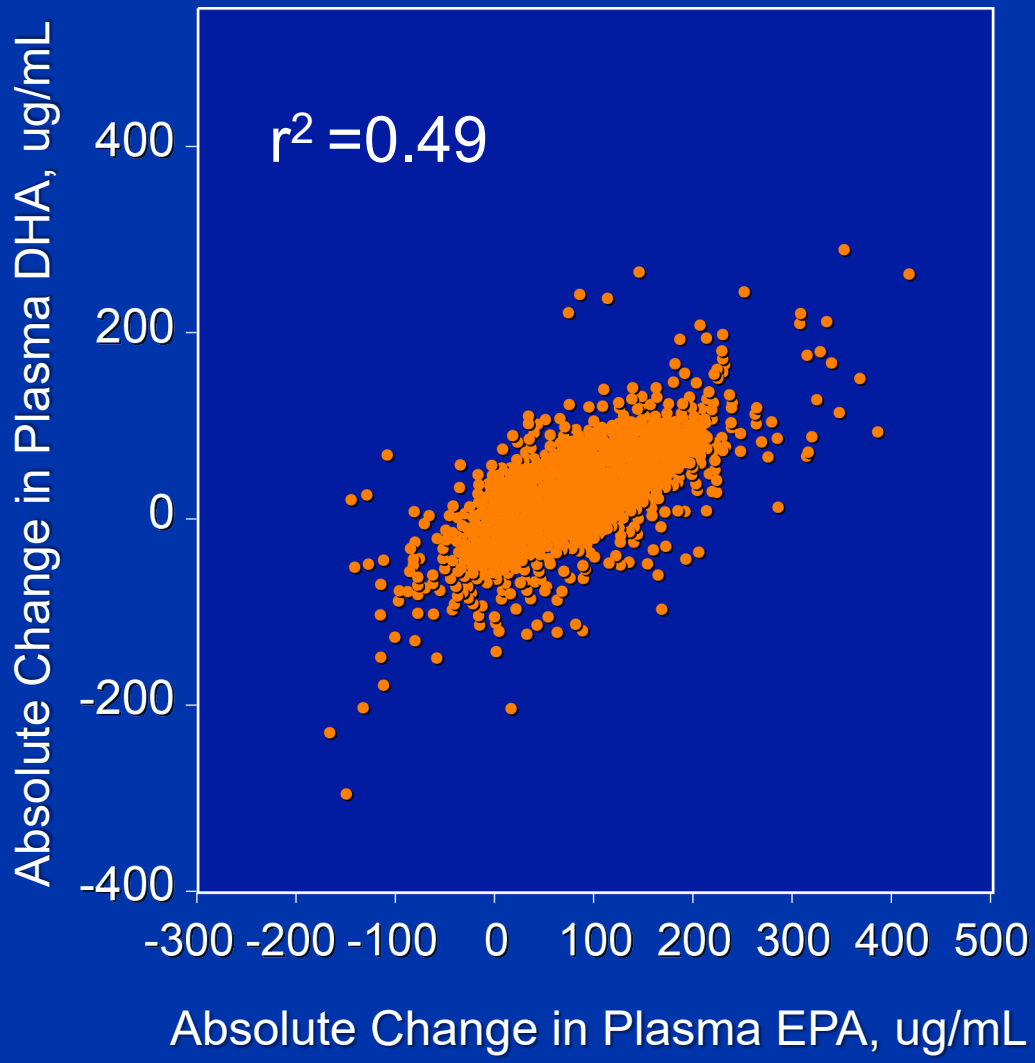


Correlation Between EPA and DHA Levels

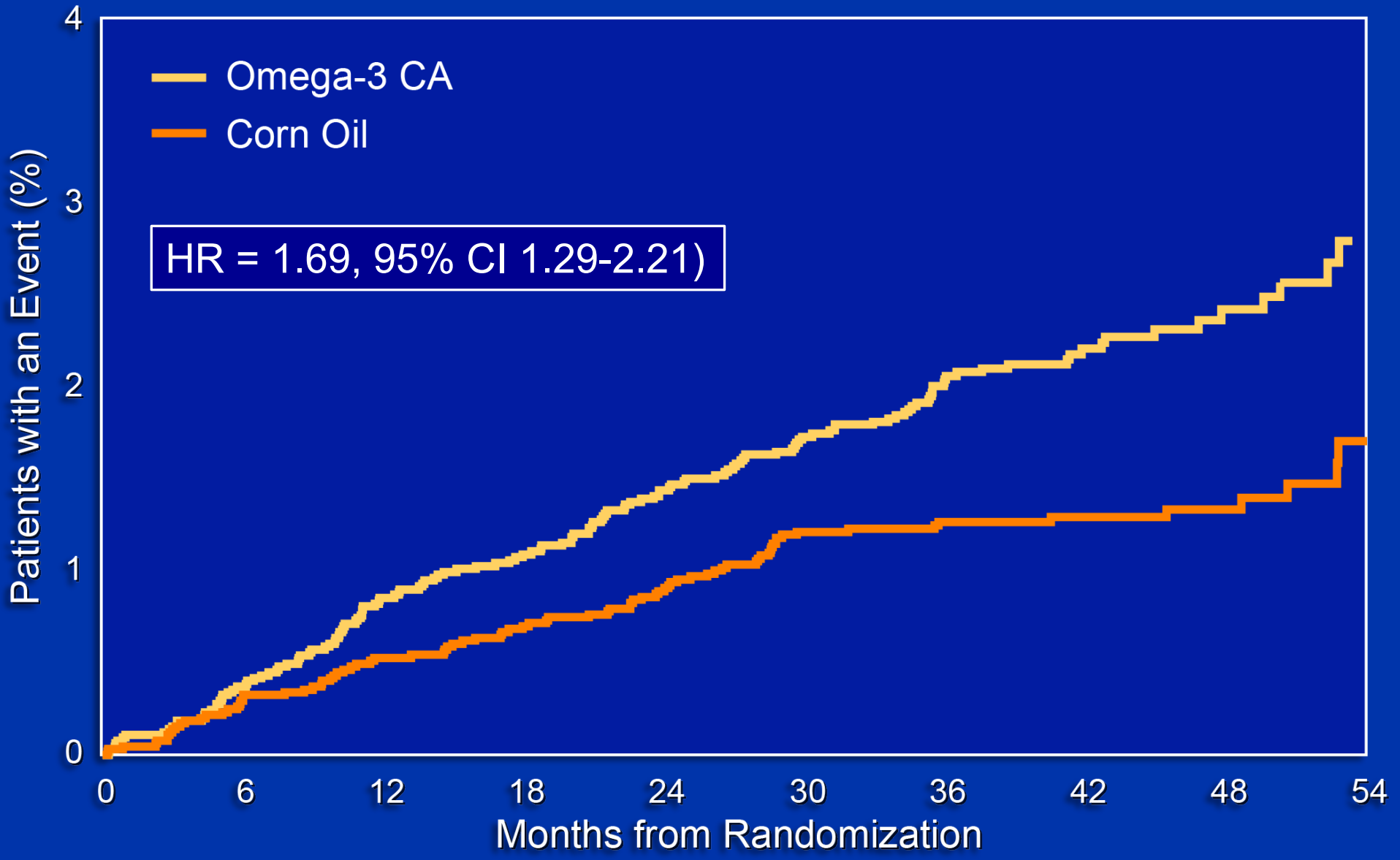
Achieved EPA vs DHA



Change in EPA vs DHA



STRENGTH: Time to Onset of Atrial Fibrillation



Limitations

1) This substudy represents a post hoc analysis that should be considered exploratory and hypothesis-generating.

2) Analysis by tertiles reduces statistical power since each group represents only 1/3 of the population (however, confidence intervals are reasonably narrow).

3) Imbalances in baseline characteristics can influence results. Although multivariable analysis was used, residual confounding is always a possibility.

4) There was a moderate correlation between EPA and DHA levels (r^2 = 0.49 to 0.55), which precludes completely independent assessment of these fatty acids and outcome.

Conclusions

- Despite a 443% increase in EPA levels with omega-3 carboxylic acid, the top tertile was not associated with any benefit.
- Despite a 68% increase, the top tertile of achieved DHA levels was not associated with harm.
- These findings, in the context of increased risk of atrial fibrillation in omega-3 trials, cast uncertainty whether there is net benefit or harm with any omega-3 preparation.
- Additional research is needed with trials designed to compare corn oil with mineral oil and to compare purified EPA with other formulations of omega- 3 fatty acids.

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Association Between Achieved ω-3 Fatty Acid Levels and Major Adverse Cardiovascular Outcomes in Patients With High Cardiovascular Risk
A Secondary Analysis of the STRENGTH Trial

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Supplemental content

IMPORTANCE In patients treated with ω-3 fatty acids, it remains uncertain whether achieved levels of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) are associated with cardiovascular outcomes.

OBJECTIVE To determine the association between plasma levels of EPA and DHA and cardiovascular outcomes in a trial of ω-3 fatty acids compared with corn oil placebo.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, multicenter trial enrolled patients at high cardiovascular risk with elevated triglyceride levels and low levels of high-density lipoprotein cholesterol at 675 centers (enrollment from October 30, 2014, to June 14, 2017; study termination January 8, 2020; last visit May 14, 2020).

INTERVENTIONS Participants were randomized to receive 4 g daily of ω-3 carboxylic acid (CA) or an inert comparator, corn oil.

MAIN OUTCOMES AND MEASURES The primary prespecified end point was a composite of