

n-3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia

The ORIGIN Trial Investigators*

ABSTRACT

BACKGROUND

The use of n-3 fatty acids may prevent cardiovascular events in patients with recent myocardial infarction or heart failure. Their effects in patients with (or at risk for) type 2 diabetes mellitus are unknown.

METHODS

In this double-blind study with a 2-by-2 factorial design, we randomly assigned 536 patients who were at high risk for cardiovascular events and had impaired fasting glucose, impaired glucose tolerance, or diabetes to receive a 1-g capsule containing at least 900 mg (90% or more) of ethyl esters of n-3 fatty acids or placebo daily and to receive either insulin glargine or standard care. The primary outcome was death from cardiovascular causes. The results of the comparison between n-3 fatty acids and placebo are reported here.

RESULTS

During a median follow up of 6.2 years, the incidence of the primary outcome was significantly decreased among patients receiving n-3 fatty acids, as compared with those receiving placebo (574 patients [9.1%] vs. 581 patients [9.3%]; hazard ratio, 0.98; 95% confidence interval [CI], 0.87 to 1.10; P=0.72). The use of n-3 fatty acids also had no significant effect on the rates of major vascular events (1034 patients [16.5%] vs. 1017 patients [16.3%]; hazard ratio, 1.01; 95% CI, 0.93 to 1.10; P=0.81), death from any cause (951 [15.1%] vs. 964 [15.4%]; hazard ratio, 0.98; 95% CI, 0.89 to 1.07; P=0.63), or death from arrhythmia (288 [4.6%] vs. 259 [4.1%]; hazard ratio, 1.10; 95% CI, 0.93 to 1.30; P=0.26). Triglyceride levels were reduced by 5 mg per deciliter (0.16 mmol per liter) more among patients receiving n-3 fatty acids than among those receiving placebo (P<0.001), without a significant effect on other lipids. Adverse effects were similar in the two groups.

CONCLUSIONS

Supplementation with 1 g of n-3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events. (Funded by Sanofi; ORIGIN ClinicalTrials.gov number, NCT00069784.)

Table 2. Primary and Other Outcomes.

Outcome	n-3 Fatty Acids (N=6281)		Placebo (N=6255)		Adjusted Hazard Ratio (95% CI)	P Value
	no. (%)	rate/100 patient-yr	no. (%)	rate/100 patient-yr		
Primary outcome: death from cardiovascular causes	574 (9.1)	1.55	581 (9.3)	1.58	0.98 (0.87-1.10)	0.72
Secondary outcomes						
Myocardial infarction, stroke, or death from cardiovascular causes	1034 (16.5)	2.92	1017 (16.3)	2.88	1.01 (0.93-1.10)	0.81
Death from any cause	951 (15.1)	2.57	964 (15.4)	2.62	0.98 (0.89-1.07)	0.63
Death from arrhythmia*	288 (4.6)	0.78	259 (4.1)	0.70	1.10 (0.93-1.30)	0.26
Other outcomes						
Fatal and nonfatal myocardial infarction	344 (5.5)	0.95	316 (5.1)	0.88	1.09 (0.93-1.27)	0.28
Fatal and nonfatal stroke	314 (5.0)	0.86	336 (5.4)	0.93	0.92 (0.79-1.08)	0.32
Hospitalization for heart failure	331 (5.3)	0.91	320 (5.1)	0.88	1.02 (0.88-1.19)	0.76
Revascularization procedure	866 (13.8)	2.54	896 (14.3)	2.65	0.96 (0.87-1.05)	0.39
Angina†	724 (11.5)	2.11	725 (11.6)	2.12	1.00 (0.90-1.10)	0.94
Limb or digit amputation for ischemia	52 (0.8)	0.14	47 (0.8)	0.13	1.09 (0.74-1.62)	0.67
Hospitalization for any cardiovascular cause	2055 (32.7)	6.87	2087 (33.4)	7.00	0.98 (0.92-1.04)	0.50

* Death from arrhythmia was a composite of sudden unexpected death, nonsudden death, unwitnessed death, or resuscitation after cardiac arrest. † Includes new, worsening, or unstable disease.

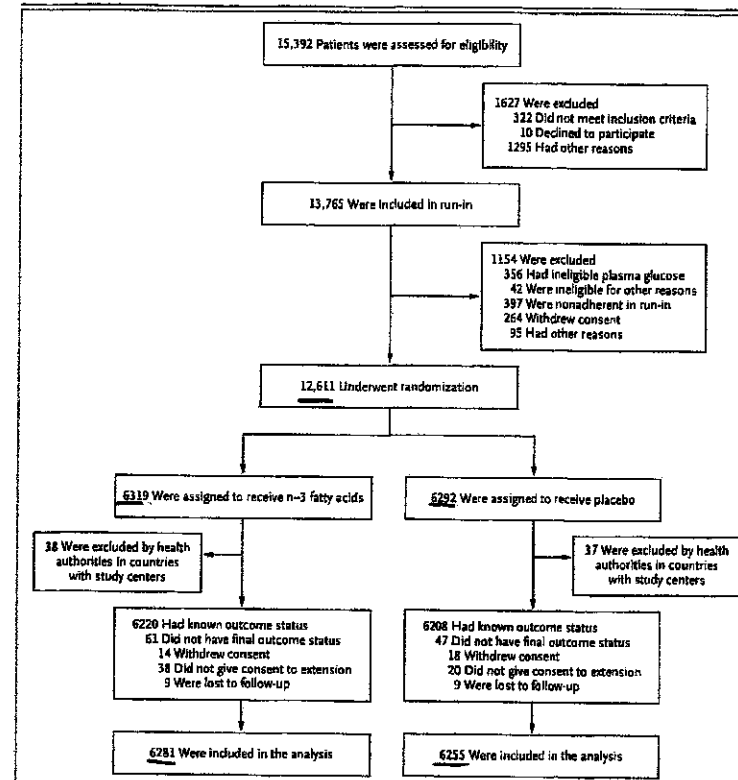


Figure 1. Enrollment and Outcomes. One participant who underwent randomization in the glucose-lowering portion of the study died before randomization to n-3 fatty acids or placebo. Data for 38 patients in the group receiving n-3 fatty acids and for 37 patients in the placebo group were excluded at the request of health authorities after site audits.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	n-3 Fatty Acids (N=6281)	Placebo (N=6255)
Age—yr	63.5±7.8	63.5±7.9
Female sex—no. (%)	2176 (34.6)	2210 (35.3)
Cardiovascular history or risk factors—no. (%)		
Myocardial infarction, stroke, or revascularization	3713 (59.1)	3664 (58.6)
Hypertension	4941 (78.7)	5021 (80.3)
Current smoking	762 (12.1)	790 (12.6)
Other risk factors—no. (%)		
Microalbuminuria or macroalbuminuria	980 (15.6)	944 (15.1)
History of cancer	279 (4.4)	274 (4.4)
Body-mass index†	29.8±5.3	29.9±5.2
Heart rate—beats per minute	69.9±12.2	69.8±12.1
Blood pressure—mm Hg		
Systolic	145.6±21.8	146.0±21.8
Diastolic	84.1±12.1	84.2±12.1
Ankle-brachial index	1.16±0.23	1.16±0.20
Cholesterol—mg/dl		
Total	189±46	190±47
Low-density lipoprotein	112±40	112±40
High-density lipoprotein	46±12	46±12
Serum creatinine—mg/dl	1.0±0.3	1.0±0.2
Estimated glomerular filtration rate—ml/min/1.73 m ²	77.1±21.5	77.5±21.1
Fasting plasma glucose—mg/dl		
Median	125	124
Interquartile range	110-148	108-148
Glycated hemoglobin—%		
Median	6.4	6.4
Interquartile range	5.8-7.2	5.8-7.2
Characteristic	n-3 Fatty Acids (N=6281)	Placebo (N=6255)
Albumin:creatinine ratio‡		
Median	5.2	5.1
Interquartile range	2.5-19.3	2.5-18.1
Triglycerides—mg/dl		
Median	142	140
Interquartile range	99-196	97-195
Dietary EPA+DHA intake—mg/day		
Median	210.0	209.3
Interquartile range	39.7-577.4	39.6-563.1
Cardiovascular medication—no. (%)		
ACE inhibitor or ARB	4320 (68.8)	4360 (69.7)
Thiazide diuretics	2180 (34.7)	2191 (35.0)
Aspirin or other antiplatelet agent	4374 (69.6)	4291 (68.6)
Anticoagulant	438 (7.0)	432 (6.9)
Beta-blocker	3314 (52.8)	3284 (52.5)
Calcium-channel blocker	1708 (27.2)	1751 (28.0)
Statins	3331 (53.0)	3408 (54.5)

* Plus-minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DHA docosahexaenoic acid, and EPA eicosapentaenoic acid. † The body-mass index is the weight in kilograms divided by the square of the height in meters. ‡ The albumin:creatinine ratio is the ratio of albumin to creatinine in the urine.

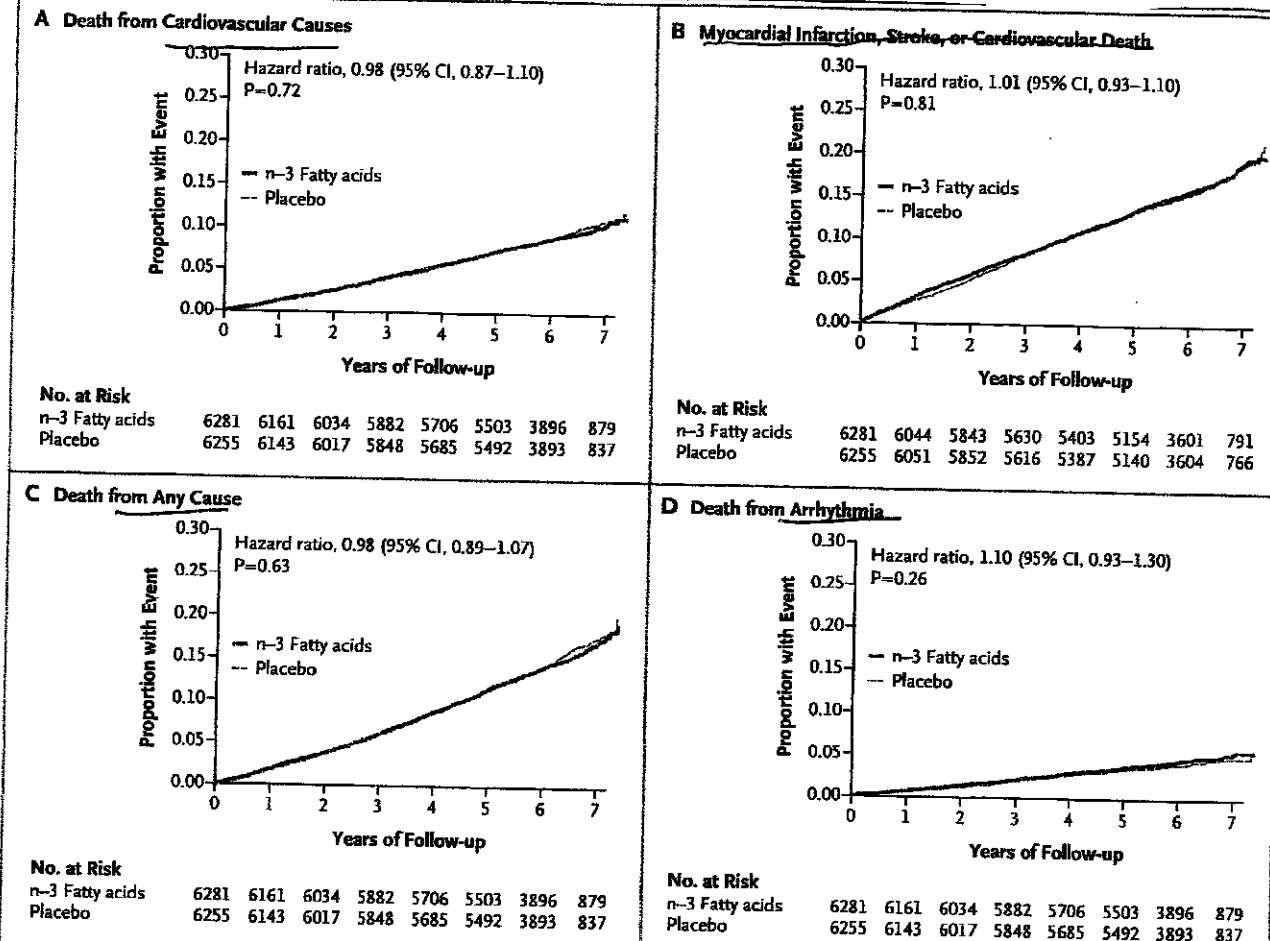


Figure 2. Primary and Secondary Outcomes. Shown are the proportions of participants with primary or secondary outcome events. The primary outcome was death from cardiovascular causes (Panel A), and the secondary outcomes were a composite of myocardial infarction, stroke, or death from cardiovascular causes (Panel B), death from any cause (Panel C), and fatal arrhythmia (Panel D).

Risk Factor	n-3 Fatty Acids (N=6281)	Placebo (N=6255)	P Value
Blood pressure (mm Hg)			
Systolic	-4.37±22.5	-4.51±22.5	0.75
Diastolic	-4.93±12.8	-4.96±13.1	0.91
Heart rate (beats/min)	-0.13±12.3	0.25±12.2	0.13
Cholesterol (mg/dl)			
Total	-15.7±1.0	-14.6±1.0	0.17
Low-density lipoprotein	-11.8±0.8	-12.4±0.8	0.44
High-density lipoprotein	-0.1±0.3	-0.2±0.3	0.78
Triglycerides (mg/dl)	-23.5±3.0	-9.0±3.0	<0.001

* Plus-minus values are means ±SD for blood pressure and heart rate and means ±SE for cholesterol and triglycerides.

Handwritten notes in Chinese:

- 0 统计与... (Statistics and...)
- 1 抗血小板 (Antiplatelet)
- 2 降压药 (Antihypertensive)
- 3 血脂 (Lipids)
- 4 血糖 (Blood glucose)
- 5 胰岛素 (Insulin)
- 6 死亡 (Death)
- 7 随访 (Follow-up)
- 8 结局 (Outcome)
- 9 结论 (Conclusion)
- 10 研究 (Study)
- 11 数据 (Data)
- 12 分析 (Analysis)
- 13 结果 (Results)
- 14 讨论 (Discussion)
- 15 总结 (Summary)