ASCEND

A randomized trial of omega-3 fatty acids (fish oil) versus placebo for primary cardiovascular prevention in 15,480 patients with diabetes

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Background

- Diabetes increases cardiovascular risk, so a safe dietary supplement that reduced risk would be of value
- Higher fish intake is associated with lower cardiovascular risk
- Omega-3 (n-3) fatty acid (FA) supplements recommended for secondary prevention based on trials done in 1980s and 1990s
- Increased fish intake recommended for primary prevention
- Recent meta-analyses of randomized trials have not shown benefits of omega-3 fatty acids in primary or secondary prevention





ASCEND trial design

- Eligibility:Age \geq 40 years; any DIABETES;no prior cardiovascular disease
- Participants: 15,480 UK patients
- **Randomization:** Omega-3 fatty acids 1 g capsule/day vs placebo (and aspirin 100 mg daily vs placebo)

Follow-up: Mean 7.4 years; >99% complete for morbidity & mortality

Adherence: Average adherence to omega-3 capsules 77%

Streamlined methods: mail-based (questionnaires & treatment); no study clinics; electronic health records; 2x2 factorial design; highly cost-effective

ASCEND Study Collaborative Group. Trials 2016;17:286 / Am Heart J 2018;198:135-144







Baseline demographics (N=15,480)

Characteristic	Omega-3 FA	Placebo
Age, years	63	63
Male	63%	63%
Type 2 diabetes	94%	94%
Diabetes duration, median years	7	7
Hypertension	62%	62%
Statin use	75%	76%
Body Mass Index, kg/m ²	31	31
Glycated haemoglobin, mmol/mol	55 (7.2%)	55 (7.2%)



Key outcomes



Primary efficacy outcome: Serious Vascular Event (SVE)

Non-fatal myocardial infarction,

Non-haemorrhagic stroke or transient ischaemic attack, or

Cardiovascular death (excluding any intracranial haemorrhage)

Secondary outcome: SVE or any revascularization

Pre-specified for subgroup analyses



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Effect of omega-3 FA supplements on serious vascular events







Effect of omega-3 FA supplements on vascular events

	Omega-3 FA	Placebo	
Type of Event	(N=7740)	(N=7740)	Rate Ratio (95% CI)
no	o. of participants	s with events (%)	
Non-fatal myocardial infarction	186 (2.4)	200 (2.6)	∎-
Non-fatal presumed ischaemic stroke	217 (2.8)	214 (2.8)	₽ →
Transient ischaemic attack	185 (2.4)	180 (2.3)	∎ →
Vascular death excl. intracranial haemorrhage	186 (2.4)	228 (2.9) —	
Any serious vascular event	689 (8.9)	712 (9.2)	0.97 (0.87–1.08)
Any arterial revascularization	368 (4.8)	356 (4.6)	P = 0.55
Any serious vascular event or revascularization	882 (11.4)	887 (11.5)	1.00 (0.91–1.09)
		0.6	0.8 1.0 1.2

Omega-3 FA Better Placebo Better





Effects of omega-3 FA supplements on SVE or revascularization in different types of participant







Effect of omega-3 FA supplements on cause-specific mortality

Cause of Death	Omega-3 FA (N=7740) no. of participan	Placebo (N=7740) ts with events (%)	Rate Ratio (95% CI)		
Coronary	100 (1.3)	127 (1.6)	B	0.79	(0.61–1.02)
All stroke	35 (0.5)	37 (0.5)	← ■	0.94	(0.59–1.50)
Other vascular	61 (0.8)	76 (1.0)	← ■	0.80	(0.57–1.12)
Vascular	196 (2.5)	240 (3.1)		0.82	(0.68–0.98)
Cancer	305 (3.9)	319 (4.1)		0.95	(0.82–1.12)
Respiratory	73 (0.9)	78 (1.0)		0.93	(0.68–1.28)
Other medical	158 (2.0)	125 (1.6)		1.26	(1.00–1.59)
External causes	17 (0.2)	22 (0.3)	← ■	0.77	(0.41–1.45)
Non-vascular	553 (7.1)	544 (7.0)	-	1.01	(0.90–1.14)
Unknown cause	3 (0.0)	4 (0.1)	<→	0.75	(0.17–3.31)
All-cause mortality	752 (9.7)	788 (10.2)		0.95	(0.86–1.05)
			0.6 0.8 1.0 1.2 1.4 1.0	6	

Omega-3 FA Better Placebo Better





Effect of omega-3 FA supplements on site-specific cancer

	Omega-3 FA	Placebo				
Type of Event	(N=7740)	(N=7740)	ntc (9/)	Rate Ratio (95% C	i)	
	no. Or particip	ants with eve		. .		
Gastrointestinal	226 (2.9)	251 (3.2)		▋	0.90	(0.75–1.07)
Respiratory	104 (1.3)	100 (1.3)			1.04	(0.79–1.37)
Genitourinary	323 (4.2)	303 (3.9)			1.07	(0.91–1.25)
Haematological	94 (1.2)	80 (1.0)	-		1.17	(0.87–1.58)
Breast	103 (1.3)	90 (1.2)	-		1.14	(0.86–1.52)
Melanoma skin	55 (0.7)	54 (0.7)			1.02	(0.70–1.48)
Other	23 (0.3)	32 (0.4)	← ■		0.72	(0.42–1.22)
Unspecified	25 (0.3)	32 (0.4)	← ■		0.78	(0.46–1.31)
Any cancer	894 (11.6)	890 (11.5)		+	1.00	(0.91–1.10)
			0.6 0.8	1.0 1.2 1.4 1.	.6	

Omega-3 FA Better Placebo Better



Fish oil supplements are widely used



- In a large UK prospective study, 31% of adults reported taking fish oils
- Estimates suggest 19 million people in the US take fish oil supplements
- Benefits claimed on: heart, brain, weight, vision, inflammation, skin, pregnancy, liver fat, depression, childhood behaviour, mental decline, allergies, bones...
- Environmental costs debated









Summary: Omega-3 FA supplementation in diabetes

- ASCEND is the largest and longest duration placebo-controlled randomized trial of omega-3 FA supplementation
- No effect on primary outcome of serious vascular events
- No effect on cancer, total or cause-specific mortality
- No safety concerns

Guideline recommendations should be reconsidered







ORIGINAL ARTICLE

Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*