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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on behalf of the ASCEND Study Collaborative Group

Funded by British Heart Foundation, UK Medical Research Council
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Designed, conducted and analysed independently of the funders
University of Oxford is the trial sponsor

Declaration of interest

- Research contracts (Merck, The Medicines Company, Bayer, Mylan)

Conclusions: 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

Fish oil supplements are widely used

- Estimated global market for omega-3 products was $31 billion in 2015
- 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…

Background

- 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 ≥ 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 & study treatment);
no study clinics; 2x2 factorial design; highly cost-effective

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

Key outcomes

Primary efficacy outcome: Serious Vascular Event (SVE)

Non-fatal myocardial infarction,

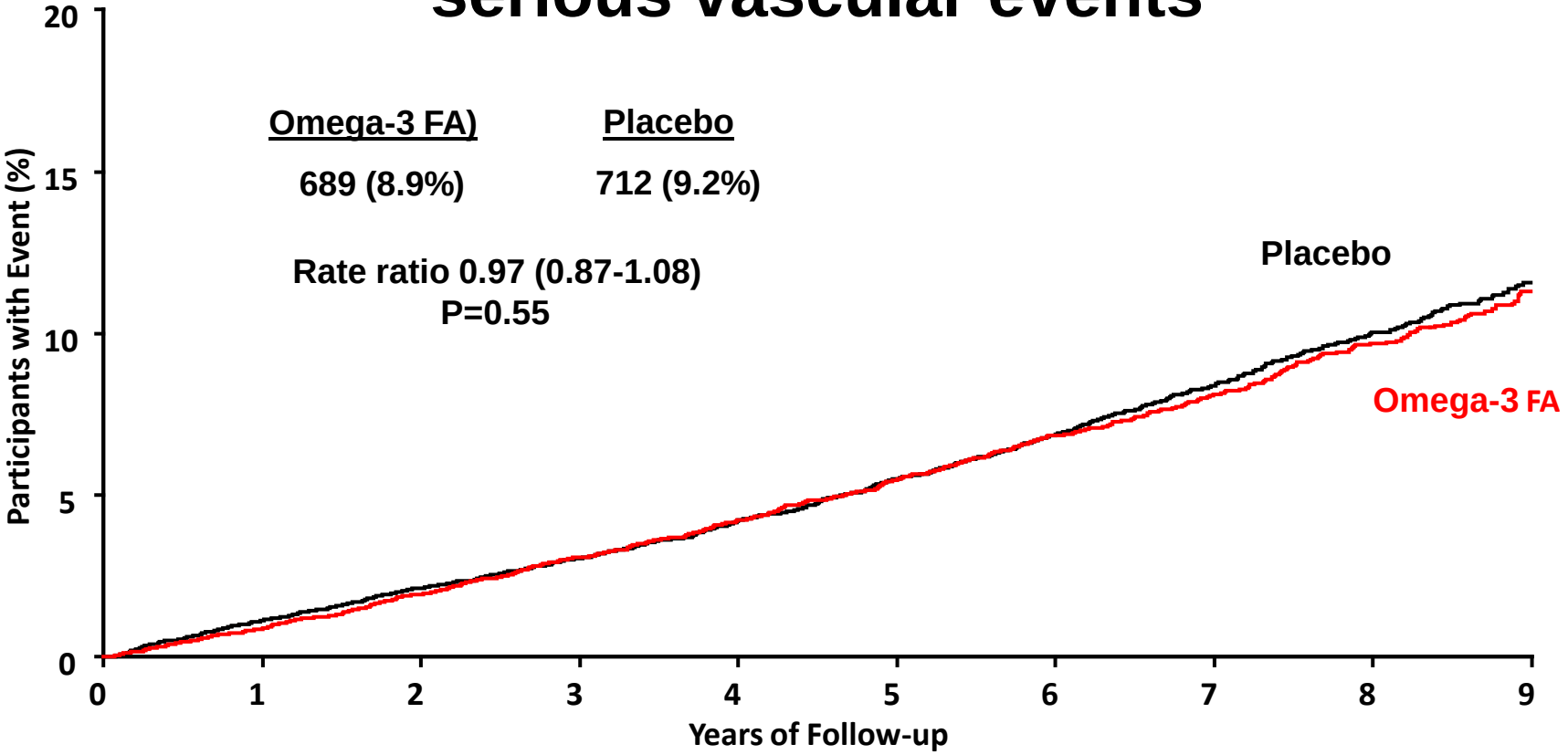
Non-haemorrhagic stroke or transient ischaemic attack, or

Cardiovascular death (excluding any intracranial haemorrhage)

Secondary outcome: SVE or any revascularization

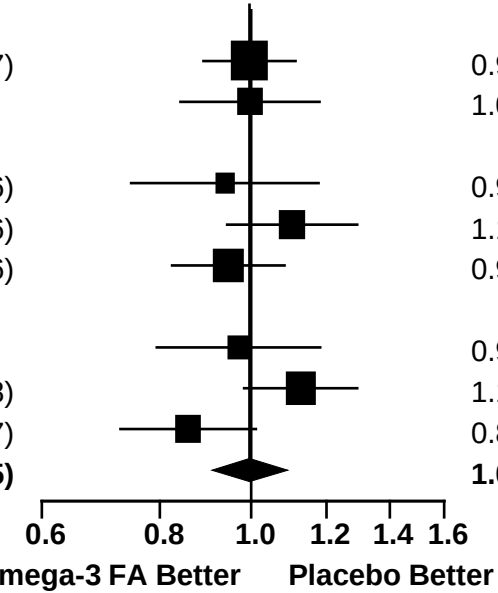
Pre-specified for subgroup analyses

Effect of omega-3 FA supplements on serious vascular events



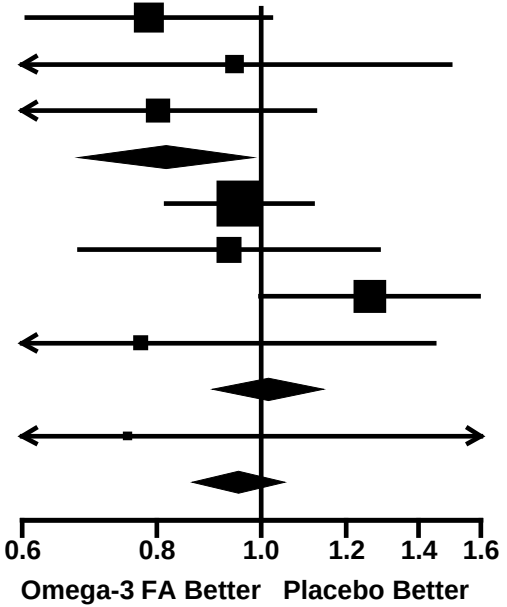
Effects of omega-3 FA supplements on SVE or revascularization in different types of participant

Baseline Characteristic	Omega-3 FA (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)
Sex			
Men	614 (12.7)	617 (12.7)	0.99 (0.89–1.11)
Women	268 (9.2)	270 (9.3)	1.00 (0.84–1.18)
Body mass index (kg/m²)			
<25	143 (12.7)	152 (13.6)	0.94 (0.75–1.18)
≥25 <30	320 (11.5)	291 (10.6)	1.10 (0.94–1.29)
≥30	393 (11.0)	418 (11.6)	0.94 (0.82–1.08)
5-year vascular risk			
<5%	192 (6.1)	195 (6.2)	0.97 (0.79–1.18)
≥5% <10%	427 (13.1)	388 (11.8)	1.13 (0.98–1.29)
≥10%	263 (19.8)	304 (22.7)	0.86 (0.73–1.01)
All	**882 (11.4)**	**887 (11.5)**	**1.00 (0.91–1.09)**



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

Cause of Death	Omega-3 FA (N=7740) no. of participants with events (%)	Placebo (N=7740) no. of participants with events (%)	Rate Ratio (95% CI)
Coronary	100 (1.3)	127 (1.6)	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)**



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ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*