Effects of omega−3 fatty acid supplements on arrhythmias in ASCEND

Sarah Parish and Jane Armitage
on behalf of the ASCEND Study Collaborative Group
Declaration of interest

- Research contracts (Grants to the University of Oxford from the British Heart Foundation, the UK Medical Research Council and Cancer Research UK)
- Others (ASCEND study drugs were provided by Solvay, Abbott, Mylan and Bayer)
Background

- Higher fish consumption is associated with lower risks of coronary heart disease, and particularly of cardiac deaths, in observational studies.

- 2018 meta-analyses of randomized trials of 0.5-2 g daily omega-3 fatty acid supplementation (EPA+DHA) did not show convincing benefit on CVD.

- Three further large trials have since reported.
Omega-3 fatty acid supplementation and coronary events in randomized trials

Aung, JAMA Cardiol 2018; ASCEND, NEJM 2018; Manson, NEJM 2019; Bhatt, NEJM 2019
Omega-3 fatty acid supplementation and coronary events in randomized trials

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Omega-3 fatty acid supplementation and coronary events in randomized trials

12 low dose studies

REDUCE-IT

Rate ratio for coronary heart disease events (95% CI)

25% reduction

Aung, JAMA Cardiol 2018; ASCEND, NEJM 2018; Manson, NEJM 2019; Bhatt, NEJM 2019
Omega-3 fatty acid supplementation and coronary events in randomized trials

12 low dose studies

Rate ratio for coronary heart disease events (95% CI)

REDUCE-IT
7% (4%-10%) reduction per 1 g daily

25% reduction

EPA + DHA daily dose, g

Aung, JAMA Cardiol 2018; ASCEND, NEJM 2018; Manson, NEJM 2019; Bhatt, NEJM 2019
Omega-3 fatty acid supplementation and coronary events in randomized trials

Aung, JAMA Cardiol 2018; ASCEND, NEJM 2018; Manson, NEJM 2019; Bhatt, NEJM 2019
Omega-3 fatty acid supplementation: outcomes in REDUCE-IT

Bhatt, NEJM 2019
Omega-3 fatty acid supplementation: outcomes in REDUCE-IT

Bhatt, NEJM 2019
Omega-3 fatty acid supplementation: outcomes in REDUCE-IT

Bhatt, NEJM 2019

- Coronary heart disease
- Atrial fibrillation or flutter (hospitalisation)

Graph showing the rate ratio (95% CI) of events in low dose trials compared to REDUCE-IT trials, with EPA + DHA daily dose, g on the x-axis and rate ratio on the y-axis.
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)

Exclusion: Current anticoagulation use

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

97% with linkage to electronic Hospital Episode Statistics data
during trial (and for 14 years before randomization)

Adherence: Average adherence to omega-3 capsules 77%

ASCEND Study Collaborative Group: Trials 2016 / Am Heart J 2018/ NEJM 2018
Arrhythmia outcomes

Arrhythmia outcomes defined from:

- Hospitalisations or serious events reported by participants during the trial
- ICD10-code diagnoses and OPCS4 procedure codes in electronic Hospital Episode Statistics data

Key outcomes considered:

- Atrial fibrillation (AF) in participants without known prior AF
- Non-fatal ventricular arrhythmia
- Any non-fatal cardiac arrhythmia
  
  \(\text{(AF, bradyarrhythmia, ventricular or supraventricular arrhythmia)}\)
- Cardiac death
# Baseline demographics (N=15,480)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 FA</th>
<th>Placebo</th>
</tr>
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<tr>
<td>Age, years</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>63%</td>
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<td>Hypertension</td>
<td>62%</td>
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<tr>
<td>Statin use</td>
<td>75%</td>
<td>76%</td>
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<tr>
<td>Body Mass Index, kg/m²</td>
<td>31</td>
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<tr>
<td>Prior admission with atrial fibrillation</td>
<td>0.7%</td>
<td>0.6%</td>
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Arrhythmia outcomes from self-report vs EHR

Numbers of participants with non-fatal arrhythmias

- **Atrial fibrillation**
  - n=1177
  - Electronic health record event during trial from Hospital Episode Statistics
  - Self-reported event during trial

- **Ventricular arrhythmia**
  - n=135
  - 9

- **Any cardiac arrhythmia**
  - n=1576
  - 1137
  - 335
  - 104
Effect of omega-3 FA supplements on arrhythmias and cardiac deaths

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<th>Condition</th>
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<td>Coronary death</td>
<td>100 (1.3%)</td>
<td>127 (1.6%)</td>
<td>0.79 (0.61, 1.02)</td>
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<td>Non-coronary cardiac death</td>
<td>33 (0.4%)</td>
<td>42 (0.5%)</td>
<td>0.78 (0.50, 1.23)</td>
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<td>Any cardiac death</td>
<td>133 (1.7%)</td>
<td>169 (2.2%)</td>
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Omega-3 FA better  Placebo better
Omega-3 fatty acid supplementation and AF in randomized trials

GISSI-HF Investigators, Lancet 2008; The Risk and Prevention Study Collaborative Group, NEJM 2013
Omega-3 fatty acid supplementation and AF in randomized trials

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Summary: arrhythmias in ASCEND

• ASCEND provides randomized evidence of the effects of 1 g daily omega-3 FA capsules on arrhythmias

• No statistically significantly effect on atrial fibrillation

• No statistically significantly effect on any non-fatal cardiac arrhythmia
Conclusions

• Evidence from 13 large trials suggests that omega-3 FA supplementation may have a dose-related protective effect on coronary events.

• May also be a dose-related adverse effect on non-fatal arrhythmias.

• Systematic reporting of arrhythmia outcomes in existing and future trials is required.

• The ongoing STRENGTH trial using 4 g daily supplementation will be able to add importantly when it completes next year.