

Effects of omega-3 fatty acid supplements on arrhythmias

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For several decades there has been interest in the possible role of omega-3 fatty acids (FAs) in the prevention of cardiovascular disease and the possibility that they have anti-arrhythmic effects. Higher consumption of fish (which contains the long-chain omega-3 FAs, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) is associated with lower risks of coronary heart disease events and particularly of cardiac deaths in observational studies, but meta-analyses in 2018 of randomized trials of ½ to 2 g omega-3 FA supplementation for a mean of 4-5 years failed to show convincing benefit on cardiovascular outcomes.¹ However, recently, the REDUCE-IT trial of a 4 g daily dose of icosapent ethyl (a purified form of EPA) among participants with high triglycerides reported a highly statistically significant 25% proportional reduction in various cardiovascular outcomes.² The results in both low and high dose large trials are consistent with a pro rata to dose reduction in coronary heart disease events of 7-8% per 1 g EPA+DHA supplementation.^{1, 2} However, in REDUCE-IT,² supplementation was also associated with a nominally statistically significant (without adjustment for multiple comparisons) approximate 50% increase in hospitalisation for atrial fibrillation (AF) or flutter. It is not clear whether this excess is reflected in the low dose trials.² In ASCEND we previously reported on the effects of omega-3 FA on participant-reported arrhythmia adverse events but here we report more comprehensively on AF and other arrhythmias, using additional data extracted from linked electronic health records.³

ASCEND was a large mail-based randomized trial which assessed the effect of 1 g omega-3 FA supplementation (containing 0.84 g EPA+DHA) daily on the risk of serious vascular events in people with diabetes but without known atherosclerotic cardiovascular disease (and, in a 2x2 factorial design, also the effects of low-dose

aspirin; current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.).³ The protocol was approved by the North West Multi-centre Research Ethics Committee and all of the participants provided written informed consent. As anticoagulant use at randomization was an exclusion criterion (because of the aspirin comparison) most people with known AF would have been excluded. The main results on omega-3 FA supplementation, reported previously, showed no significant effect on the primary outcome.³ This investigation includes added data extracted from electronic record linkage to hospital episodes, available for 97% of participants both during the trial and for 14 years before randomization.

Arrhythmia outcomes were defined based on either hospitalisations or serious episodes reported by the participants during follow-up or from ICD-10 diagnoses or OPCS4 procedure codes in the electronic data. AF diagnoses in hospital episodes prior to randomization were used to define prior known AF. Arrhythmia outcomes considered are AF (among participants without any known prior AF) and non-fatal ventricular arrhythmia. We only considered non-fatal ventricular arrhythmias, with survival to the next day, because we could not reliably ascertain all arrhythmias contributing to death, and it was not possible to determine which cardiac arrests without resuscitation had involved an arrhythmia. Therefore, we also consider the outcome cardiac deaths overall, which would include sudden deaths due to fatal cardiac arrhythmias (see Arrhythmia Outcome Definitions on the ASCEND study web page: <https://ascend.medsci.ox.ac.uk/professionals>). Statistical methods are as used in the main study report.³ P-values <0.01 were considered statistically significant in this secondary analysis.

Among 15 480 participants randomized in ASCEND less than 1% had a prior hospital admission with an AF diagnosis. Among the remaining 99%, AF was recorded from either electronic health records or participant reports in 1177 participants, compared to 287 by self-report alone. AF occurred in 7.7% of participants in the omega-3 FA group and in 7.6% in the placebo group, with a non-significant rate ratio (RR) of 1.02 (95% confidence interval [CI] 0.91-1.15). A non-fatal ventricular arrhythmia was recorded in non-significantly more participants in the omega-3 FA group than in the placebo group (81 vs. 54, RR 1.49, 95% CI 1.06 to 2.09, P=0.02). Most (106/135) of the non-fatal ventricular arrhythmias required intervention (resuscitation, ablation or implantable cardioverter-defibrillator); sensitivity analyses restricting to these ventricular arrhythmias yielded a similar RR of 1.90 (95% CI 1.30 to 2.77). Cardiac death occurred in fewer participants in the omega-3 FA group than in the placebo group (1.7% vs. 2.2%; P=0.04).

The 47% proportional excess of hospitalisation for AF observed in REDUCE-IT with 4 g daily supplementation corresponds to a 10 (95% CI 3 to 18)% proportional excess per 1 gram, and two other of the 10 large low-dose trials have reported on AF and found non-significant positive associations with hospitalisation for AF (Figure).^{2, 4, 5} The association in the low dose trials, including ASCEND, in combination is not statistically significant but does not exclude the level of effect per gram seen in REDUCE-IT.

In conclusion, evidence from large trials now suggests that omega-3 FA supplementation may have a dose-related protective effect on coronary events. However, systematic reporting of arrhythmia outcomes in existing and future trials is

required to clarify whether supplementation also has any adverse effects on non-fatal arrhythmias.

Writing Committee (on behalf of the ASCEND Study Collaborative Group)

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Data Access

Proposals for data access will be considered by the ASCEND Steering Committee in accordance with the trial protocol. Procedures for accessing the data are available at: <https://www.ndph.ox.ac.uk/files/about/ndph-data-access-policy-1.pdf>.

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SP, MM, AO, JB, KW, WS, GB, RH, RC, LB and JA work in the Clinical Trial Service Unit & Epidemiological Studies Unit of the Nuffield Department of Population Health at the University of Oxford. The Clinical Trial Service Unit & Epidemiological Studies Unit has a staff policy of not taking any personal payments directly or indirectly from industry (with reimbursement sought only for the costs of travel and accommodation to attend scientific meetings). It has received research grants from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, The Medicines Company, Merck, Mylan, Novartis, Pfizer, Roche, Schering, and Solvay, which are governed by University of Oxford contracts that protect their independence. SP and RC are co-inventors of a genetic test for statin-related myopathy risk but receive no income from it.

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FIGURE LEGEND

Figure. Effects of omega-3 fatty acid supplementation on atrial fibrillation in large trials. The atrial fibrillation (AF) outcomes were: GISSI-HF,⁴ among participants without ECG evidence of AF at randomization, AF in the ECGs taken at each visit during the trial or an event between visits causing or worsening heart failure/hospitalisation; Risk and Prevention Study,⁵ hospitalisation for AF; ASCEND, new onset of AF; REDUCE-IT,² hospitalisation for AF or atrial flutter. The risk ratio and confidence interval in REDUCE-IT were estimated from the reported percentages getting the outcome in each group and the P-value (3.1% vs. 2.1%, supplementation vs. placebo, P=0.004).

Rate ratio
for atrial
fibrillation
(95% CI)

