Cardiovascular disease: Omega-3 fatty acid supplements in secondary prevention

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A meta-analysis of 14 RCTs of omega-3 fatty acid supplementation in the secondary prevention of cardiovascular disease found it did not reduce the risk of cardiovascular events or all-cause mortality. This is consistent with the limited role for omega-3 fatty acid supplements outlined in NICE guidance.

Overview and current advice

NICE guidance recommends a limited role for omega-3 fatty acid supplements in the secondary prevention of cardiovascular disease. NICE clinical guideline 48, Myocardial infarction (MI): secondary prevention states¹:

- Patients should be advised to consume at least 7 g of omega-3 fatty acids per week from two to four portions of oily fish.

- For patients who have had an MI within 3 months and who are not achieving 7 g of omega-3 fatty acids per week, consider providing at least 1 g daily of omega-3-acid ethyl esters treatment licensed for secondary prevention post MI for up to 4 years.

- Initiation of omega-3-acid ethyl esters supplements is not routinely recommended for patients who have had an MI more than 3 months earlier.

This guideline, including the section on fish diet and omega-3 fatty acid supplementation, is currently being updated, with publication expected November 2013.

The current recommendation was based on results from the GISSI-Prevenzione Investigators (GISSI-P) trial, which showed a benefit of treatment with omega-3 fatty acid supplementation within 3 months of an MI². However, as discussed in the NICE guideline, there were limitations with this trial and further research in this area was needed. GISSI-P was an open-label randomised controlled trial (RCT), not controlled with placebo, in which other secondary prevention treatment, in particular statins, had not been optimised. A meta-analysis by Kwak et al has recently reconsidered the issue of omega-3 fatty acid supplementation in the secondary prevention of cardiovascular disease³.
New evidence

This meta-analysis included 14 double-blind, placebo-controlled RCTs of omega-3 fatty acid supplements in patients with a history of cardiovascular disease (n=20,485). 4 RCTs were exclusively in post-MI patients (n=9,228); other RCTs included patients with stable coronary heart disease, implanted cardioverter defibrillator, chronic heart failure (CHF), peripheral arterial disease or stroke. Study size varied from 59 to 6,975 participants; follow-up ranged from 1.0 to 4.7 years.

The main analysis looked at the association between omega-3 fatty acid supplementation and the risk of overall cardiovascular events (angina, sudden cardiac death, cardiovascular death, CHF, peripheral vascular disease, transient ischaemic attack and stroke, fatal and non-fatal MI and non-scheduled cardiovascular interventions). Supplementation did not reduce this risk to a statistically significantly extent compared with placebo; relative risk (RR) 0.99, 95% confidence interval [CI] 0.89 to 1.09. It also did not statistically significantly reduce the risk of all-cause mortality or most of the individual cardiovascular endpoints. There was a statistically significant reduction in cardiovascular death (RR 0.91; 95% CI 0.84 to 0.99). However, this was no longer statistically significant when a study with major methodological problems was excluded (RR 0.92; 95% CI 0.35 to 1.01).

This meta-analysis had several limitations, notably diverse patient populations, a wide range in study size, and a wide time period over which the studies were conducted. Also, the cardiovascular events used in the meta-analysis were not always the primary outcome of the included studies.

The meta-analysis excluded 2 large RCTs because they had an open-label study design without the use of placebo, which can introduce bias. Both these RCTs, GISSI-Prevenzione (n=11,324) and the Japan EPA Lipid Intervention study (JELIS) (n=18,645), found omega-3 fatty acid supplements were beneficial in reducing cardiovascular events. However, when a supplementary meta-analysis was performed including these additional studies, there was no statistically significant reduction in overall cardiovascular events (RR 0.95; 95% CI 0.87 to 1.03).

The main meta-analysis included 3 RCTs from 2010, all of which showed no benefit with omega-3 fatty acid supplementation on cardiovascular events. An accompanying editorial discusses that these newer trials were each substantially underpowered and unable to detect small to modest benefits on cardiovascular events. This is because of their smaller sample size (n=2,501, n=4,837, n=3,851) and lower-than-expected event rates. Other secondary prevention treatments, for example statins, were much more widely used in these later trials meaning that any benefit of omega-3 fatty acid supplementation would be harder to detect.

Commentary

Commentary provided by Dr Anthony Wierzbicki, Consultant in Metabolic Medicine/Chemical Pathology, Guy’s & St Thomas’ Hospitals, London:

Annually, approximately 650,000 items of omega-3 fatty acid compounds (Omacor and Maxepa) are prescribed in primary care in England, at a cost of about £15.4m. Variation between PCTs is marked. In March 2012, the lowest prescribing PCT prescribed 66 items of at a cost of £1,761 compared with 5,660 items at a cost of £79,598 in the highest prescribing PCT.

Omega-3 fatty acid supplements are used for two indications. In the first, large doses of purified omega-3 fatty acids (docosahexaenoic acid [DHA] or eicosapentaenoic acid [EPA]) are used to reduce triglycerides in a dose-proportional manner. There are meta-analyses that support this use but no trials have been performed to investigate the effects of high-dose omega-3 fatty acids on cardiovascular events in this population.

The second more common use of omega-3 fatty acid supplements is at low doses for cardiovascular disease prevention. Evidence for dietary-based omega-3 supplementation is controversial – especially in regard of how to interpret the large DART-2 trial which showed increased cardiovascular events with fish supplementation. A close review of the dietary evidence suggests that if there is any
cardiovascular benefit, it is associated with eating some fish as opposed to not eating fish at all. NICE guidelines for secondary prevention post-MI and lipid modification (which are both currently being updated) recommend consuming oily fish.

The data for the use of pharmacological supplements of omega-3 fatty acids is based on the GISSI-P and JELIS studies, where they reduced cardiovascular events in primary and secondary prevention. However, the benefits occurred in the context of inadequate and/or changing statin therapy. The issue of inadequate statin therapy in these patients is far more significant than the open-label design of these studies.

Recently, the ORIGIN study in 12,536 patients with impaired fasting glucose, impaired glucose tolerance or type 2 diabetes showed no benefit of omega-3 fatty acid supplementation on cardiovascular events. ORIGIN was included in a recent meta-analysis of 20 trials that showed no benefit of omega-3 fatty acid supplementation on cardiovascular events.

In summary, NICE guidance already recommends only a limited role for omega-3 fatty acid supplements. NICE guidelines on secondary prevention post-MI and lipid modification are currently being updated and will consider this issue within these updates.

References
9. NHS Business Services Authority: personal communication July 2012
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