Is the tide going out on fish oil supplements for CVD?

Angus Thompson MSc(ClinPharm), BPharm(Hons), GradDip(PrescSci), CGP

Ever since the rarity of ischaemic heart disease among the Inuit people was linked with their consumption of high levels of n-3 polyunsaturated fatty acids (n-3 PUFAs),¹ we have been encouraged to consume oily fish as part of our diet to try and reduce the burden of cardiovascular disease (CVD).

Science certainly tells us that the n-3 PUFAs, which are commonly found in oily fish, do possess a range of biological properties including antithrombotic, anti-inflammatory and triglyceride-lowering effects.² Given that these properties have the potential to reduce the development and progression of CVD, adopting Inuit habits appears logical and this message has become ingrained as a cornerstone of the advice regarding a healthy diet.

Human beings are by nature, however, often on the look-out for an easy option. Consequently with cost, effort and personal taste being barriers for many to change their eating habits, fish oil supplements have been widely adopted as the way many people try and attain the ‘Eskimo effect’.

The perception of these consumers that they are doing the right thing is of course reinforced by the packaging, marketing and in some cases an endorsement from organisations promoting cardiovascular health.

It should, of course, be noted that fish oil products are not only taken by those who seek cardiovascular benefits. Many perceive that there are musculoskeletal system benefits, and indeed there is evidence that rheumatoid arthritis can be helped. Others take fish oil for a variety of reasons; indeed, I recently visited a lady at home to be met by the smoothest handshake I have ever had the pleasure of, which she attributed wholly to the magic of a daily fish oil capsule. There have also been suggestions that n-3 PUFAs may be beneficial for cognitive function and mood.

The evidence regarding some of these other indications is a fascinating topic in its own right, but outside the scope of this article.

Figure 1. Despite their popularity, current trial evidence does not support the use of fish oil supplements to reduce cardiovascular morbidity or mortality

Angus Thompson weighs up the evidence for taking daily fish oil supplementation in the primary and secondary prevention of heart disease.

Is the tide going out on fish oil supplements for CVD?
So what does the research tell us about the impact of n-3 PUFA supplementation on meaningful cardiovascular endpoints for the average Westerner.

Patients with established CVD

GISSI-P

Although n-3 PUFA supplements have been in use for the management of hypertriglyceridaemia for many years, they gained a new foothold in orthodox medicine around 10 years ago with the publication of the GISSI-Prevenzione trial (GISSI-P). This study found that supplementation with 1g per day of n-3 PUFA ethyl esters, when given to those who had recently experienced an MI, reduced cardiovascular and overall death.3

This evidence was sufficient to influence the 2007 NICE guidance on secondary prevention of MI, with the recommendation that a supplement be considered for patients who could not achieve the desired intake through diet.4

GISSI-HF

In the GISSI-Heart Failure (GISSI-HF) trial, n-3 PUFA were given to a population with chronic heart failure (NYHA class II–IV), the majority of whom were already being treated with guideline-recommended therapies such as ACE inhibitors and beta-blockers.5 After a median follow-up of 3.9 years, the study reported a small benefit in terms of overall mortality (27 per cent with n-3 PUFA vs 29 per cent with placebo) and hospitalisation rates.

Alpha Omega and OMEGA

The Alpha Omega and OMEGA trials evaluated the effect of n-3 PUFAs on populations similar to that in the GISSI-P trial, namely those who had experienced an MI, although the findings conflict with those of the study published a decade previously.

Alpha Omega evaluated the effect of supplementary n-3 PUFAs (and/or alpha-linolenic acid) in the form of a margarine. After 40 months, it was reported that n-3 PUFA supplementation did not significantly reduce the rate of major cardiovascular events.6

The OMEGA trial used the same (1g per day) supplement given in the GISSI-P and GISSI-HF trials, and after one year of follow-up the rates of sudden cardiac death and total mortality were not statistically different among those taking supplements or placebo.7

So what can we draw from the conflicting evidence in the post-MI setting? The most plausible explanation is the rapid evolution of standard care for those who have experienced an acute coronary event, both in the immediate and secondary prevention phases. For example, whereas when the GISSI-P trial started recruitment only around 5 per cent of patients were receiving statins, over 90 per cent of those in the OMEGA trial were discharged from hospital taking these medicines.

The reality is that, as standard care has improved and rates of recurrent events and death have fallen, it has become increasingly hard for an add-on therapy such as n-3 PUFAs to show an additional benefit.

Critics of these two studies could argue that the follow-up period in OMEGA was insufficient and that the mean dose (376mg per day) of n-3 PUFAs in Alpha Omega was low; consequently it remains debatable whether a higher dose given for longer would have shown beneficial effects in the context of contemporary post-MI management.

SU.FOL.OM3

Work by the SU.FOL.OM3 Collaborative Group goes some way to answering this question. This trial evaluated the effect of a supplement containing 600mg n-3 PUFAs in a group of patients with a range of established cardiovascular diagnoses, including MI, unstable angina and stroke.8

The findings of this French study were consistent with Alpha Omega and OMEGA in that the primary outcome measure of major cardiovascular events (composite of nonfatal MI, stroke or death from cardiovascular disease) was not significantly reduced by the use of the supplement, in this case given for a median of 4.7 years.

Primary prevention

However the majority of people taking n-3 PUFA supplements do not have heart failure and have not experienced an MI or stroke – they are people who wish to stave off heart and circulatory disease in the future. Nonetheless, given a historic lack of data to specifically inform decisions in this population, there has been something of a tendency to extrapolate the messages from other research, in particular the early epidemiological studies.

With two new trials throwing light on the role of n-3 PUFAs in lower-risk populations, there is no longer any need to
make such leaps of faith – we have some hard data on primary prevention.

**ORIGIN**
The ORIGIN trial recruited patients with diabetes or prediabetes and compared a daily dose of 1g n-3 PUFAs with placebo over a median follow-up period of 6.2 years. Supplementation did not reduce the rate of the primary outcome, death from cardiovascular causes, or a range of other end-points such as major cardiovascular events or overall death (see Figure 2).

These findings occurred despite a modest reduction in triglyceride levels, elevation of which is recognised as common among those with diabetes.

**The Risk and Prevention Study Collaborative Group**
This most recent trial also compared a daily 1g supplement of n-3 PUFAs with placebo in terms of the effects on a population with multiple cardiovascular risk factors and in some cases evidence of atherosclerotic vascular disease, but without prior MI. After five years it was again found that n-3 PUFAs did not reduce the rate of cardiovascular morbidity or mortality.

**Cancer risk**
Some of those with a fondness for fish oil supplements have reassured themselves that while there might not be any clear benefit for heart and circulatory health, there really was no risk of harm. However, this idea has been challenged.

While we know that n-3 PUFAs may increase the risk of bleeding, as would be expected from their antiplatelet effect, this is generally not a major problem for the majority of people, with the possible exception of those on antithrombotics where an enhanced effect may be seen.

What has recently surfaced, however, is a concern regarding cancer risk. Now let us be clear: a causative link has not been shown and there are logical arguments as to why fish oil could actually be expected to have antineoplastic effects, but a study finding an increased risk of prostate cancer among men taking supplements cannot simply be dismissed.

Further research is certainly needed, but in the meantime clinging onto the comfort blanket of an idea that fish oil ‘does no harm’ seems hard to justify.

**Conclusion**
While most of the recent trials regarding the effects of n-3 PUFAs on CVD do not support the widespread level of supplementation seen in many countries, there remain some gaps in the evidence base. Whether the ongoing ASCEND and VITAL trials will see the tide wash in some more favourable evidence for fish oil and other sources (eg krill) of n-3 PUFAs remains to be seen.

**References**

**Declaration of interests**
None to declare.

Angus Thompson is a lecturer in therapeutics and pharmacy practice at the School of Pharmacy, University of Tasmania, and a practising Home Medicines Review and hospital pharmacist.