Omega-3 Marine Polyunsaturated Fatty Acids
Post-myocardial Infarction

Introduction

It was first hypothesised in 1956 by Hugh Sinclair that a relative deficiency of essential fatty acids, especially EPA+DHA, was a cause of atherosclerosis. This causes accumulation of cholesterol as cholesteryl esters (oleate and linoleate) in arterial intima. There is local synthesis of cholesterol in the intima and greater influx of low density lipoproteins due to increased vascular permeability. Sinclair’s hypothesis was largely ignored until Danish researchers in the 1970s suggested that very low rates of cardiovascular disease in Greenland Inuits were due to the very high intake of marine fat rich in EPA and DHA. A low level of plasma EPA and EPA/arachidonic acid (AA) ratio were first suggested as a new coronary risk factor in 1986.

Epidemiological studies have consistently demonstrated fish intake being associated with a reduced risk of coronary heart disease (CHD) and stroke (CVA). Consumption of one to three serves of fish per month is associated with an 11% reduction, and five serves per week a 38% reduction, of death due to CHD. In a more recent systematic review that involved 1,035,416 participants, fish intake was associated with 6% lower all-cause mortality. In addition, there

Take Home Messages

- A high fish intake and/or an Omega-3 Index ≥8% is associated with a very low risk of sudden cardiac death, compared to those with low or no fish intake or an Omega-3 Index of ≤4%.
- Supplementation with marine Omega-3 has been variably shown to reduce cardiovascular events.
- Supplementation most benefits patients with a low marine Omega-3 intake and a low Omega-3 Index ≤4%, or impaired left ventricular function (EF <50%).
- Absorption of EPA+DHA is enhanced if taken with fatty food.
- Side-effects of Marine Omega-3 occur in less than 5% of people and are minor.
- The National Heart Foundation of Australia and the American Heart Association recommend Marine Omega-3 1000mg/day post AMI and as second line therapy in patients with heart failure.
Hormonal Contraception Trouble-shooting Part One: The Overweight Woman

Clinical Trial Results

The first major clinical endpoint trial of supplemental marine n-3 in patients post-infarction was the GISSI-P Trial which was published in 1999. The trial involved 11,324 patients who were followed for 3.5 years. This trial used Omega-3 acid ethyl esters (EPA+DHA) 822mg per day. Results showed a clear decrease in cardiovascular events, and in particular, sudden cardiac death.

Further analysis showed that the benefit of Omega-3 supplementation was confined to those patients with impaired left ventricular function. This was confirmed in a quasi-randomised post-bypass study published in 2011.

Sudden Cardiac Death and Ejection Fraction in the of GISSI-P Study

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Cardiologists were encouraged to give their patients 2000mg of an ethyl ester EPA+DHA preparation. In a follow-up of 2,100 patients 44% were commenced on 2000mg of an ethyl ester EPA+DHA supplement. The supplement group had a 45% lower death rate over three years (4.5% vs 8.5%, p=0.02). If baseline EF was <40%, there was a 64% reduction (p=0.007) over the three years. Over 60% of patients were on statins.

In the Japan EPA Lipid Intervention Study (JELIS) of 18,645 patients, 3,664 had established coronary heart disease and all were on statin therapy – the first such study. Patients were randomised to receive 1,800mg EPA/day or placebo and followed for 4.6 years. The incidence of major CHD was lower in the EPA group compared to the placebo group (8.7% vs 10.7% p=0.02).

The results of more recent clinical intervention with relatively low-dose (1000mg or less EPA+DHA/day) supplemental marine omega-3 trials have been neutral regarding prevention of recurrent coronary events.

Omega-3 Marine Polyunsaturated Fatty Acids Post-myocardial Infarction

Coronary Heart Disease Mortality and Fish Intake

2 meta-analyses of case-control or cohort studies over 200,000 individuals follow-up mean 12 years.

1 serve = 200gm fish

was a dose response: for every 200mg of EPA+DHA consumed there was a 7% lower all-cause mortality.8

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In September 2018, results of the Reduce-It trial were announced. This is now the third high-dose omega-3 outcome trial completed and statistically the most robust. There were 8,179 statin-treated patients followed for 4.9 years. Patients had either CHD or were at high risk for CHD, the active group were given 4,000mg of an ethyl ester EPA per day. There was a 25% relative risk reduction of major coronary events (p<0.001) among the active group.

There have been at least three reviews of supplemental fish oil over the last year. These included asymptomatic individuals and patients with CHD. Different conclusions have been made using the same published data! This confusion is discussed in ‘appendix’. The most recent review of trials up to April 2017 was ‘negative’ and was published in August 2018 under the ‘Cochrane’ banner.

In the brief discussion of the statistical findings, the authors demonstrated poor understanding of the physiology of the essential fatty acids EPA+DHA and the reasons for clinical trial discrepancies. Most concerning, no reference was made to the 2017 comprehensive review by the AHA.

Very different conclusions were made by the AHA experts. Unfortunately, a number of marine omega-3 supplementation studies since GISSI-P have not shown the same benefit. These neutral studies have been underpowered due to low dose, small numbers, and there has been no assessment of blood levels.

**Recommendations of NHFA and AHA**

The skill set to interpret trials of supplementation of an essential nutrient is wider than that needed to assess a typical drug or device trial. Ideally investigators should have expertise in nutrition, cardiology, clinical trial management and statistics.

In 2002, the AHA recommended that all patients with documented CHD consume 1000mg of EPA+DHA, preferably from oily fish and, if this were not possible, from supplements. A 100g serve of an oily fish, such as salmon, gives approximately 1000mg of combined EPA+DHA. In 2008, an Expert Committee of the National Heart Foundation of Australia (NHFA) made the same recommendations. The NHFA committee noted ‘in recent years intervention trials trend towards no effect.’ Therefore, support for use recommendation was C; ‘some support for recommendation – (s) best care should be its application.’

In 2017 the AHA update extended their earlier recommendations to include Omega-3 supplementation in patients with heart failure. In the update, it was noted that ‘…most recent trials in post-myocardial infarction patients were substantially underpowered to detect a clinically meaningful effect on CHD death, with even less power to detect an effect … on the risk of sudden cardiac death.’

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*Sudden Cardiac Death Risk Related to Omega-3 Index*

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<th>Omega-3 Index (%)</th>
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<th>Higher</th>
</tr>
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<tr>
<td>&lt;4 USA, India, Brazil</td>
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<td>&gt;8 Japan, Greenland, Norway</td>
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<td>4-6 Australia, France, Spain</td>
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There is a 90% lower risk of death with an Omega-3 index of >8 compared to <4


*(adapted by Ms Samantha Kitchen for the author, from the sources listed)*
Finally, it was noted that ‘Benefits also could be greater in certain subsets of patients with CHD such as those with low ejection fraction or low circulating levels of Omega-3 PUFA from marine sources.’

**Omega-3 Index**

We now have a robust measure of adequate dose-response called the Omega-3 Index. This is a measure of the proportion of EPA+DHA fatty acids in the phospholipid membrane of red blood cells as a proportion of all fatty acids in the membrane. This has been validated to reflect tissue levels in the myocardium, in atherosclerotic plaque, in the brain and other organs. After a change of diet and supplementation is implemented, a steady state Omega-3 Index is reached after approximately three months.

Multiple epidemiological studies show that an Omega-3 Index of ≥8% are associated with very low risk of sudden cardiac death, compared to an Index of ≤4%.

Clinical trials of supplementation, such as the JELIS Trial, have documented that cardiovascular outcomes are inversely proportional to plasma phospholipid levels, irrespective of whether a patient was in the supplemented or non-supplemented group. This makes sense from first principles. It is not the dose, but the level in the myocardium, and importantly, in the cell membrane, that stabilises against ventricular tachycardia and ventricular fibrillation induced by ischaemia, hence affecting the risk of sudden cardiac death.

It has been well established in multiple epidemiological studies that an Omega-3 Index of ≥8% is associated with very low risk of sudden cardiac death, compared to an Index of ≤4%. In fact, the risk of sudden cardiac death is 90% lower in those with the higher Omega-3 Index compared to the lower Index. The threshold of 8% is robust, and consistent across multiple population groups with multiple ethnic backgrounds. There are multiple pathways responsible for the benefit.

Maki et al in 2017 assessed effectiveness of supplemental marine Omega-3 in those 14 trials (n=71,899) in which sudden cardiac death was measured. Overall, treatment decreased sudden cardiac death by 8% (p=0.015). But only 28% of subjects had more than 1gm of EPA+DHA/day. If the daily dose of EPA+DHA was greater than 1gm/day, there was a 12.9%-29.1% lower risk of sudden cardiac death (p<0.05).

In a recent review of Omega-3 Indexes in 19 cohorts and 45,000 individuals comparing CHD mortality rates, CHD mortality would have been reduced by about 30% moving from an Omega-3 Index of 4% to 8%.

**Bleeding Risk**

There is an unfortunate medical myth that suggests that adding Omega-3 fatty acids increases bleeding risk, especially when added to aspirin and clopidogrel. This was perpetuated by Cooper et al in the recent Cochrane review. This is an important issue for patients following an acute myocardial infarction.

This issue was assessed 1,523 patients from 24 US centres in the TRIUMPH study. Rates of serious bleeding were assessed. No relationship between the Omega-3 Index (<4%, 4%-8% and >8%) and bleeding was found.

A retrospective analysis of 182 patients on treatment with high-dose fish oil (3gm per day), aspirin and clopidogrel. There was a control group of those treated with just aspirin and clopidogrel. During the follow-up, there was one major and four minor bleeds (2%) in the fish oil group versus seven (3.9%) in the control group (p=0.5).

In short, high-dose Omega-3 fatty acids in combination with aspirin and clopidogrel did not increase the risk of bleeding in those on aspirin or clopidogrel. The fear of increased bleeding risk is unscientific, but the Therapeutic Goods Administration review in 2010 stated: ‘… mindful of the theoretical risk of bleeding … and that it would be reasonable discontinuing fish oil therapy four to seven days before elective procedures.’

The 2008 NHFA report noted marine n-3 PUFA has no significant effect on bleeding time, bleeding post-surgery, nor on INR in warfarin-treated patients.
In 2010 an Australian government medicine safety update of fish oil noted the 2008 NHFA review and confirmed safety and specifically that there was only a ‘theoretical possibility of increased bleeding … not reflected functionally in results of human studies.’

In 2017, a review of 52 publications, 20 involving perioperative surgical patients, concluded that the use of ‘fish oil supplements … was not reflected in increased bleeding or blood transfusions either during or after surgery’. The 2017 AHA review stated, ‘it is noteworthy … there was little evidence of major adverse effects, such as stroke or bleeding associated with Omega-3 PUFA supplementation.’

Marine Omega-3 Intake and Blood/Tissue Levels

Until recently the tissue or blood level response to a fixed dose of Omega-3 fatty acids could not be measured conveniently. It was presumed that a fixed dose of 1000mg or less of EPA+DHA would be adequate for cardiovascular protection. However, it is now known that a dose of 1000mg of EPA+DHA on average in a typical Western population will shift only about half the patients into an intermediate or ‘safer’ zone, greater than 8% Omega-3 Index. However, as mentioned by von Schacky, one of the pioneers in the field: ‘The inter-individual variability in response to a fixed dose of EPA+DHA has been found to be large, that is [it can] vary by up to a factor of thirteen. This fact alone suggests individualising the dose given in a trial in order to reach a predefined target range of the HS-Omega-3 Index, e.g., 8%-11%.

The time is soon at hand when we will be able to treat our patients with precise therapeutic doses of Omega-3 fatty acids by measuring the response (Omega-3 Index) and titrating the dose up or down as needed.

In short, we need to measure the response to dietary or supplemental Omega-3 to know whether a patient is adequately treated. The measurement of a response to treatment is good scientific practice.
This is what we do with statins, antihypertensives and diabetic drugs.

Fortunately, a robust and accurate method will be soon available in Australia using a dried blood spot technique. This was developed in Australia in 2014 for clinical research and will be available (for a private fee) at major pathology companies or at major pharmacy chains, similar to other point-of-care testing.

EPA/DHA and CVD Prevention

General Mechanisms

Electrophysiological: Membrane stabilisation increases VF threshold
Anti-platelet (act on first voltage dependent sodium channels and the L-type calcium channels)
Lipid and Haemostatic (lowers triglycerides, non-HDL-cholesterol)
Lowers plasma leptin levels
Anti-inflammatory (Resolvins, Protectins)
Anti-atherosclerosis
Mood effects (suppresses depression)
Improves Endothelial Function
Lowers BP and Heart Rate and improves HR variability
Improves platelet sensitivity in aspirin and Clopidogrel resistance

NHFA 2008 Review www.nhfs.org.au
(This table is the intellectual property of the author)

Summary

1. At least 1000mg Omega-3 EPA+DHA per day should be given to patients post-myocardial infarction.

2. Greatest benefit in those with:
   a. Low Omega-3 Index ≤4%
   b. Ejection fraction <50% (endorsed by NHFA and AHA)
   c. High dose EPA+/-DHA (greater than 1000mg/day)

3. Enhance the absorption of EPA+DHA by taking with fatty food.

4. Measure the baseline Omega-3 Index, and 2-3 months later assess adequacy of this dose (available in the future throughout Australia).

5. No significant interaction with drug therapy.

6. Only minor side-effects exist. Less than 5% of patients complain of a fishy taste or loose motions. There is no significant risk of bleeding nor heavy metal poisoning (if <1000 capsules/day!).

7. EPA+DHA are ‘essential’ fatty acids and a relative deficiency of these may contribute to atherosclerosis and acute coronary events.

Declaration

Associate Professor David Colquhoun was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author.

The author declares no significant competing financial, professional or personal interests that might influence this article. His aim for this article is scientific clarity to help improve patient care. His is co-author of NHFA’s two articles on Omega-3 fatty acids published in 2008 and 2015.

References


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