Omega-3 fatty acids for cardiovascular protection

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Omega-3 fatty acids from fish and fish oils offer a practical complementary strategy for the treatment and prevention of cardiovascular disease. Fish should be part of a healthy diet low in saturated fats for everybody, with additional administration of omega-3 fatty acid supplements for specific groups of patients.

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The cardioprotective action of omega-3 fatty acids was first noted in the Inuit [(formerly known as Eskimos)] in Greenland, in whom a low incidence of heart disease was associated with a high intake of seafood.[1] Numerous studies since have confirmed this finding, suggesting that omega-3 fatty acids in fish and fish oils reduce the risk of illness and death from heart disease. Specific effects of omega-3 fatty acids in the cardiovascular system have been identified that help to explain how these fatty acids might act, thereby adding confidence to their use in evidence based practice.[2]

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What are omega-3 fatty acids?

Omega-3 and omega-6 fatty acids are known as essential fatty acids as they cannot be synthesised by the body and must be obtained from the diet. They are polyunsaturated fatty acids (PUFAs). The number following 'omega' represents the position of the first of the multiple double bonds in the fatty acid, counting from the terminal methyl group of the molecule.

The three main omega-3 fatty acids are:

- alpha linolenic acid (ALA; which has 18 carbon atoms and three double bonds); present in various seeds, nuts and beans and the oils derived from these (such as flaxseed, canola, walnut and soybean) and in green leafy vegetables
- eicosapentaenoic acid (EPA; with 20 carbon atoms and five double bonds); present in fish
- docosahexaenoic acid (DHA; with 22 carbon atoms and six double bonds); present in fish.

Linoleic acid (LA: 18 carbon atoms and two double bonds) is the primary omega-6 fatty acid, and is present in high levels in our modern diet. Most plants and vegetable oils in our diet (grains and sunflower, safflower and soybean oils, for example), and also the meat of animals fed grains, are rich in linoleic acid.

EPA and DHA are the biologically active omega-3 fatty acids. The human body can convert ALA to EPA and DHA by elongation of the fatty acid chain and the addition of double bonds. However, linoleic acid uses the same enzymes in the production of its longer chain fatty acid derivative arachidonic acid (the precursor to a group of proinflammatory and prothrombic compounds). The high levels of this competing omega-6 fatty acid in our modern diet make conversion of ALA to EPA and DHA inefficient. Hence, EPA and DHA are best derived directly from seafood and fish oil.

What are their cardiovascular effects?

Omega-3 fatty acids have many biochemical and physiological actions that may contribute to their cardiovascular protective effects. Fatty acids comprise 80% of all cell membranes and increasing the intake

of EPA and DHA produces corresponding increases within cell membranes, in exchange for other PUFAs. Excitable cells (such as in the brain, retina, heart and muscles) have high proportions of omega-3 fatty acids, especially DHA.

The incorporation of omega-3 fatty acids into cell membranes alters the properties of membrane receptors and ion channels, and modifies cell signalling and formation of prostaglandins, leukotrienes, thromboxane and prostacyclin, which are all derived from fatty acids by enzyme action within cells. Incorporation of EPA and DHA into platelets and vascular endothelium has an anti-ischaemic effect through reduced formation of thromboxane (proaggregatory, vasoconstrictor) while maintaining the activity of prostacyclin (antiaggregatory, vasodilator). This antithrombotic effect is considered to mediate some of the protection against acute cardiac events. The inflammatory leukotrienes implicated in atherosclerosis are derived from omega-6 fatty acids, whereas the corresponding omega-3 derived products are less active. Cell membrane incorporation of DHA is particularly high in the heart, with the effects of slowing heart rate and reducing the likelihood of triggering fatal arrhythmias, thus providing protection against sudden cardiac death. Experimentally, cardiac oxygen consumption is also reduced, which would contribute to an anti-ischaemic effect.[3]

Even small additional intakes of the omega-3 fatty acids reduce heart disease mortality after myocardial infarction, although they do not have much effect on the classic cardiovascular risk factors, suggesting direct effects in the myocardium.[4] In cohort studies, the regular consumption of fish one to two times per week is associated with reduced risk of primary sudden death (–50%), incident heart failure (–20%) or incident atrial fibrillation (–28%), compared with those who eat fish less than once per month.[5-7]

Omega-3 fatty acids can also lower high blood pressure by enhanced vasodilation and reduced vasoconstriction (improved vascular endothelial function) and by reduced sympathetic nervous system activity. In addition, they lower triglycerides and reduce platelet aggregation, attenuating these cardiovascular disease risk factors independently of changes in serum cholesterol, which is minimally affected. However, they appear to modulate heart function directly, through their incorporation into cell membranes of cardiac cells in the pacemaker region (where they have the effect of reducing spontaneous heart rate and increasing heart rate variability) and into cell membranes of contractile cells (where they have the effect of reducing the risk of spontaneous depolarisation and arrhythmia). High resting heart rate and low heart rate variability are independent markers of risk of sudden cardiac death.

How effective are they?

Two distinct patterns to the cardiovascular effects of the omega-3 fatty acids are emerging, associated with high and low doses.

Omega-3 fatty acids at high doses (more than 3 g/day EPA plus DHA) are very effective at lowering plasma triglycerides, especially in hypertriglyceridaemia. The required doses are only obtainable through supplementation. High doses also reduce platelet reactivity (antithrombotic effect), lower blood pressure slightly (by 2 to 3 mmHg) and reduce restenosis after coronary angioplasty. Despite a high bleeding tendency observed in the Inuit and experimental evidence of reduced platelet aggregation and thrombosis, the dose levels required to inhibit thrombosis and reduce blood pressure are usually higher than the intakes that are associated with a low risk of heart disease.[5]

Direct effects on the heart to reduce heart rate and the risk of sudden death or heart failure are associated with the regular intake of low doses of omega-3 fatty acids (less than 1 g/day EPA plus DHA).[4-6,9] Other large prospective epidemiological studies show reductions in cardiovascular mortality with similar regular low intakes.[2]

A new cardiovascular risk factor, the Omega-3 Index, has recently been proposed as a biomarker of cardiac omega-3 status that can be measured from a blood sample.[10] This index – the EPA plus DHA content of red blood cells expressed as a percentage of the red blood cell membrane fatty acids – is based on the fatty acid composition of red blood cells reflecting long term intake of EPA and DHA. It is inversely associated with risk for coronary heart disease mortality. Analysis of large clinical studies has shown that EPA plus DHA content in red cell membranes exceeding 6% of membrane fatty acids (that is, an Omega-3 Index of 6%) is associated with a reduced risk of cardiac events and can be achieved by as little as 0.5 g EPA plus DHA per day.[10] Further research is currently under way to validate this as a clinical biomarker.

Sources of omega-3 fatty acids

To achieve the levels of DHA and EPA required for cardioprotection, it is usually necessary for patients to consume a diet rich in fish or to take fish-derived omega-3 fatty acid supplements.

In choosing or prescribing a supplement it is important to consider the amount of DHA and EPA in the supplement. There is considerable variability in the DHA and EPA contents of different fish and different omega-3 supplements. Recent TGA compositional guidelines (November 2004) suggest that fish oil should contain at least 34% EPA plus DHA, but many fish oil capsules currently available in Australia contain less than this. Technical advances in processing have allowed the development of highly purified and concentrated omega-3 supplements, but with such advantages come concomitant increases in price. Omega-3 supplements from algal

sources have recently become available (these are suitable for vegans), but to date they contain only DHA (that is, no EPA). Increasingly, advanced encapsulation technology has allowed foods to be enriched with DHA and EPA, which provides valuable quantities in staple foods such as bread, milk, yoghurt and juices to supplement the diet and complement intake from fish.

The best source of omega-3 fatty acids remains fish and other seafood incorporated into a balanced diet. Oily fish such as salmon, tuna, sardine and mackerel have the highest quantities, and substantial amounts are retained in canned fish. However, it has been shown that fried fish and fish burgers do not confer the same cardioprotective benefits associated with omega-3 fatty acids as fish that has not been fried.[6,9]

The American Heart Association recommends the following intakes of omega-3 fatty acids:[2]

- patients without heart disease should eat fish (preferably oily) at least twice per week and also include in their diets vegetable oils and plant foods containing ALA, such as flaxseed, canola, walnuts and soybean
- patients with heart disease should have an intake of about 1 g of EPA plus DHA per day, preferably from fish but from supplements if necessary
- patients requiring triglyceride lowering may take 2 to 4 g EPA plus DHA per day as capsules, under medical guidance.

The National Heart Foundation of Australia is expected to release its recommendations regarding omega-3 fatty acid intakes this year.

How are they used?

In Australia, omega-3 fatty acid supplements and fish oils in capsule form containing 300 mg/g EPA plus DHA or more are widely available over the counter in pharmacies, health food stores and supermarkets. In the UK, some other European countries and the USA, highly purified formulations containing up to 850 mg/g EPA plus DHA are available by prescription for adjuvant treatment in secondary prevention after myocardial infarction and for treatment of hypertriglyceridaemia.

The dose required for treatment of elevated triglycerides is about two to four times higher than that used for secondary prevention after myocardial infarction. The dose recommended by the American Heart Association and the European Society of Cardiology for secondary prevention of myocardial infarction is 1000 mg of DHA plus EPA per day. For primary prevention, the dose recommended by the International Society for the Study of Fatty Acids and Lipids is 650 mg of EPA plus DHA per day.

Fish should be considered as part of a healthy diet low in saturated fats for everybody, whereas additional administration of omega-3 fatty acid concentrates would be considered for specific groups of patients.[8] The flowchart on page 64 summarises the role of omega-3 fatty acids in the treatment and prevention of cardiovascular disease.

Precautions, interactions and what needs monitoring?

Consumption of fish oil capsules may be associated with gastrointestinal side effects such as reflux or belching with a fishy taste or breath odour. Side effects vary with different fish oils and may sometimes be reduced simply by changing the supplement. Taking the supplement at night can minimise the impact of some side effects.

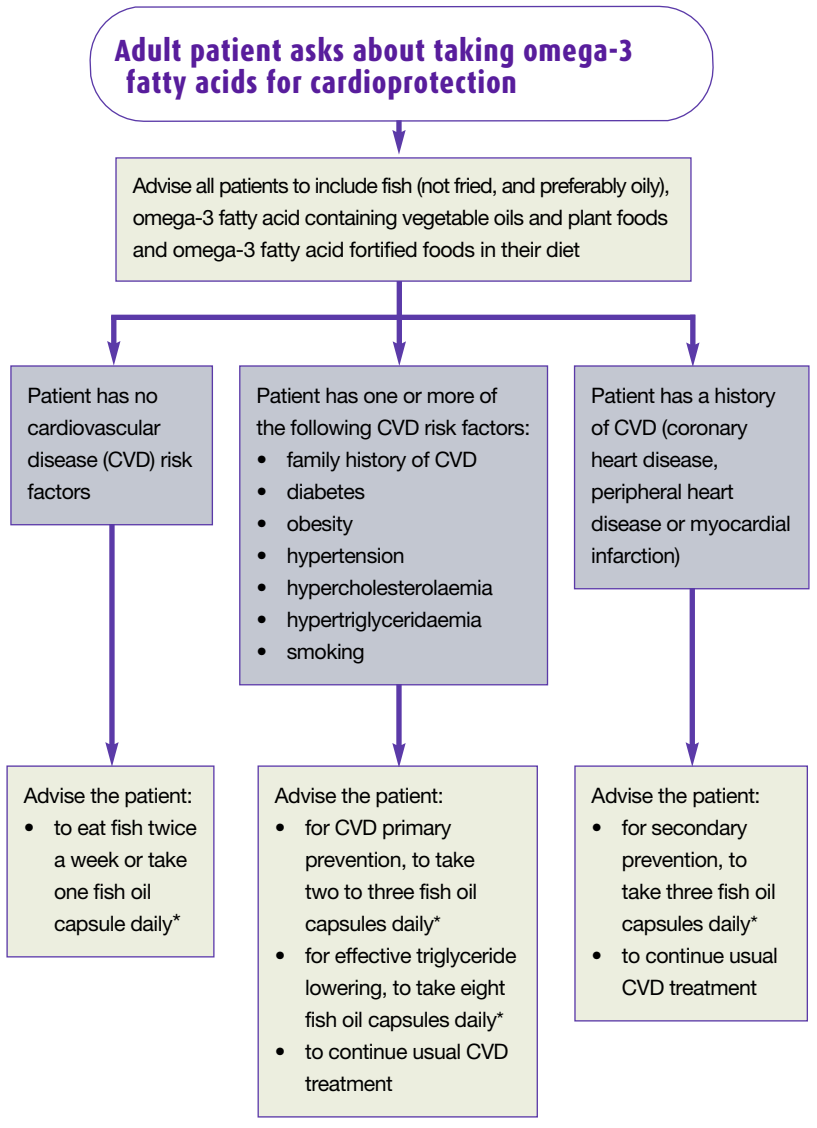
High doses of fish oils may be associated with increased LDL cholesterol, particularly in hypertriglyceridaemic patients. Despite early concerns, fish oils have little or no effect on glycaemic control or HbA_{1c}. Although the risk of clinical bleeding is low, patients taking high doses of omega-3 fatty acids who are taking oral anticoagulant therapy or at elevated risk of haemorrhage should

be monitored. In patients with hepatic impairment, aspartate aminotransferase and alanine aminotransferase levels should be monitored.

Conclusion

Omega-3 fatty acids from fish and fish oils offer a practical complementary strategy for the treatment and prevention of cardiovascular disease. With evidence available for a wide variety of cardiovascular actions, it is likely that the benefits are not derived from any one effect. Moreover, the greatest effect may be derived simply through the correction of an inadequacy in the modern western diet, an action that could be of benefit to many people. MT

Use of omega-3 fatty acids in treatment and prevention of cardiovascular disease[2]



* Fish oil capsule = 1 g capsule containing at least 300 mg/g docosahexaenoic acid plus eicosapentaenoic acid.

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DECLARATION OF INTEREST: Professor McLennan and Dr Owen have received donations of oils for research purposes and research funding support from several fish oil manufacturers.