CME

Omega-3 fatty acids

Their beneficial role in cardiovascular health

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ABSTRACT

OBJECTIVE To examine evidence for the role of omega-3 fatty acids in cardiovascular disease.

QUALITY OF EVIDENCE PubMed was searched for articles on the role of omega-3 fatty acids in cardiovascular disease. Level I and II evidence indicates that omega-3 fatty acids are beneficial in improving cardiovascular outcomes.

MAIN MESSAGE Dietary intake of omega-3 fatty acids has declined by 80% during the last 100 years, while intake of omega-6 fatty acids has greatly increased. Omega-3 fatty acids are cardioprotective mainly due to beneficial effects on arrhythmias, atherosclerosis, inflammation, and thrombosis. There is also evidence that they improve endothelial function, lower blood pressure, and significantly lower triglycerides.

CONCLUSION There is good evidence in the literature that increasing intake of omega-3 fatty acids improves cardiac outcomes. Physicians need to integrate dietary recommendations for consumption of omega-3 fatty acids into their usual cardiovascular care.

RÉSUMÉ

OBJECTIF Relever les données sur le rôle des acides gras oméga-3 dans les maladies cardiovasculaires.

QUALITÉ DES PREUVES On a consulté PubMed, à la recherche d'articles sur le rôle des oméga-3 dans les maladies cardiovasculaires. Il existe des preuves de niveaux I et II indiquant que les oméga-3 ont un effet favorable sur les issues cardiovasculaires.

PRINCIPAL MESSAGE Au cours des 100 dernières années, la consommation des acides gras oméga-3 a diminué de 80%, pendant que celle des oméga-6 augmentait considérablement. Les oméga-3 sont cardioprotecteurs en raison surtout de leurs effets bénéfiques sur les arythmies, l'athérosclérose, l'inflammation et la thrombose. Selon certaines données, ils améliorent aussi l'activité endothéliale, diminuent la tension artérielle et causent une baisse significative des triglycérides.

CONCLUSION Il existe dans la littérature des preuves convaincantes indiquant qu'une consommation accrue d'acides gras oméga-3 améliore les issues cardiaques. Le médecin devrait incorporer aux soins cardiovasculaires habituels des recommandations pour encourager la consommation des oméga-3.

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During the last decade, the amount of research on omega-3 fatty acids has increased substantially. As a result, new guidelines recommend that patients at risk of cardiovascular (CV) disease increase their dietary intake of omega-3 fatty acids. This article looks at the role of omega-3 fatty acids of marine (eicosapentenoic acid [EPA], docosahexaenoic acid [DHA]) and plant (alpha-linolenic acid [ALA]) origin in CV health in order to bring family physicians up-to-date on current evidence.

Quality of evidence

Studies providing level I, II, and III evidence of the benefits of omega-3 fatty acids are reviewed in this article. MEDLINE was searched using the words "omega-3 fatty acids" and "fish oil" combined with "hypertension," "coronary artery disease," and "hypertriglyceridemia." Trials involving humans were chosen.[1-16]

Omega-3 and omega-6 fatty acids

The lipids essential for health are the omega-3 and omega-6 polyunsaturated fatty acids (PUFA).[17] Interest in omega-3 fatty acids began in 1972. Studies by Bang and Dyerberg[3] showed that Greenland Inuit who consumed a diet high in protein and fat (mainly from fish) had significantly lower total cholesterol ($P<.005$), low-density lipoprotein (LDL) ($P<.02$), and triglyceride ($P<.005$) levels than most other people had.

Since then, much has been learned about the interaction of omega-6 and omega-3 fatty acids in CV disease and about the ratio between omega-6 and omega-3 fatty acids.[18,19] Dietary intake of omega-3 fatty acids has decreased, and dietary intake of omega-6 fatty acids has substantially increased during the last 100 years due to greater use of vegetable oils high in omega-6 fatty acids.[18,20] The ratio of omega-6 to omega-3 was about 1.5:1 as recently as 200 years ago and now is estimated at 16:1 in the average North American diet.[18] This has resulted in a diet high in omega-6 fatty acids and deficient in omega-3 fatty acids.[21]

Omega-6 and omega-3 fatty acids compete for the same enzymes. An increase in the diet of one decreases metabolism of the other.[22] Omega-6 fatty acid metabolites result in prostaglandins that are inflammatory; omega-3 fatty acids result in prostaglandins that are anti-inflammatory. The actions of omega-3 fatty acids on the CV system are listed in **Table 1**.[1,2,23-33] Omega-3 fatty acids have antiarrhythmic effects, including preventing atrial fibrillation[23,24]; antithrombotic action[25]; antiatherogenic effects[26]; anti-inflammatory effects[27,28]; and the ability to improve endothelial function,[29] lower blood pressure,[1,2] lower triglyceride levels,[30] increase high-density lipoprotein (HDL) levels,[31] and decrease apolipoprotein B-100.[32]

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

Table 1. Cardiovascular effects of omega-3 fatty acids

CARDIOVASCULAR EFFECT	MECHANISM
Antiarrhythmic	Improves membrane fluidity[23] Prevents atrial fibrillation[24]
Antithrombotic	Inhibits platelet aggregation[25]
Antiatherogenic	Inhibits intimal hyperplasia[26]
Anti-inflammatory	Reduces production of omega-6 proinflammatory eicosanoid (prostaglandin)[27] Reduces C-reactive protein[28]
Improves endothelial function	Direct effect on endothelial vasomotor function[29]
Lowers blood pressure	By the 3 previous cardiovascular effects[1,2]
Improves lipid parameters and cardiovascular risk parameters	Inhibits synthesis of hepatic triglycerides and very low-density lipoprotein resulting in lower triglyceride levels[30] Raises high-density lipoprotein levels[31] Lowers apolipoprotein B-100 levels[32]

Data from Din et al.[33]

Hypertension

Trials are listed in **Table 2**.[1-16] Geleijnse et al[1] did a meta-analysis of 36 randomized trials (22 of which were double blind) carried out between 1966 and 2001 (level I evidence). The meta-analysis showed that consuming an average of 3.7 g/d of fish oil reduced systolic blood pressure (BP) by 2.1 mm Hg ($P<.01$) and diastolic BP by 1.6 mm Hg ($P<.01$). The BP-lowering effects were greater in people older than 45 years and in those whose BP was higher than 140/90 mm Hg.

A meta-analysis (level I evidence) done by Appel et al[2] found a significant reduction in BP (5.5 mm Hg systolic BP and 3.5 mm Hg diastolic BP) in untreated hypertensive patients taking supplements of more than 3 g/d of omega-3 PUFA. High doses were required to achieve these results, and patients' acceptance of the fishy taste and subsequent belching was poor ($P<.001$). Most trials lasted less than 3 months, so the long-term benefits are unclear.

Heart disease

Bang and Dyerberg[3] and Dyerberg et al[4] did epidemiologic studies (level II evidence) to establish the cardioprotective

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Table 2. Characteristics of studies on use of fish oil

STUDIES	SUBJECTS	DESIGN	*P* VALUE	COMMENTS
HYPERTENSION				
Geleijnse et al[1]	Weighted according to size of trial	Meta-regression analysis of 36 trials (22 were double-blind)	<.01	Large doses of fish oil required
Appel et al[2]	291 untreated hypertensive patients	Meta-analysis of 17 controlled clinical trials	<.01	Patients' acceptance of fishy taste and belching was poor (P<.001) Long-term efficacy was unclear
HEART DISEASE				
Bang and Dyerberg[3]	130 Greenlandic Eskimos living on the west coast of Greenland	Epidemiologic study	<.005 <.02 <.005	Lower triglyceride, total cholesterol, low-density lipoprotein, and very low-density lipoprotein levels
Dyerberg et al[4]	316 Greenlandic Eskimos living in Denmark		<.01	Significant increase in HDL levels in men (~40%); nonsignificant increase in women
Dewailly et al[5]	422 men and 495 women, all James Bay Cree	Epidemiologic study	<.02	Increased intake of omega-3 fatty acids had a positive effect on hypertension and ischemic heart disease
Diet and Reinfarction Trial (DART)[6]	2033 men	RCT	<.05	29% reduction in 2-year all-cause mortality
Lyon Diet Heart Study[7]	605 men	Secondary prevention trial	<.0002	Three end points examined (see text)
Indo-Mediterranean Diet Heart Study[8]	1000 patients	Single-blind RCT	<.001	Three end points examined (see text)
GISSI-Prevenzione trial[9,10]	11 324 patients	Open-label RCT	.01	Risk of sudden cardiac death reduced most
Bucher et al[11]	15 806 patients: 7951 in intervention groups; 7855 in control groups	Meta-analysis of 11 trials	<.001 <.001 <.01	Reduction in overall mortality, fatal myocardial infarction, and sudden cardiac death
Nilsen et al[12]	300 patients with a high intake of fish	Double-blind crossover trial	Not significant <.0001 <.0016	Secondary prevention of cardiac events Lower triglyceride levels Higher HDL levels
FAMILIAL HYPERTRIGLYCERIDEMIA				
Richter et al[13]	12 patients	Open-label trial	<.01	Small trial showed significant reduction
Pschierer et al[14]	8 patients	Open-label trial	<.01	Small trial
HMG-COA REDUCTASE INHIBITORS				
Nakamura et al[15]	19 patients	Open-label trial	<.01 <.05 <.01	Raised HDL level Lowered total cholesterol Lowered triglyceride levels by 50%
CARDIOVASCULAR SURGERY				
Eritsland et al[16]	610 patients	RCT	<.034	Studies using higher doses have not shown significant benefit

HDL—high-density lipoprotein, RCT—randomized controlled trial.

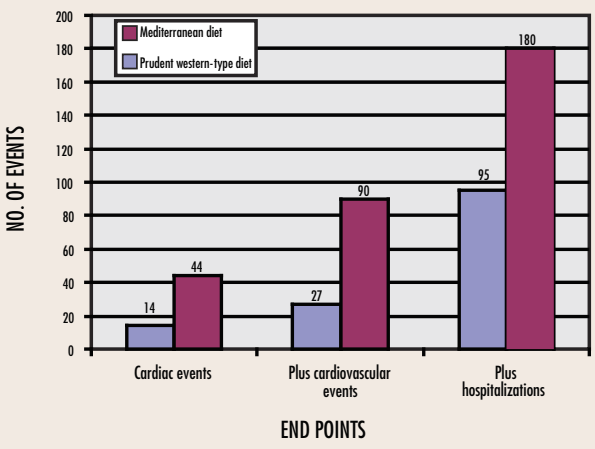
effects of omega-3 fatty acids from marine sources in the Inuit people of Greenland in the 1970s. Despite a high-fat diet, the incidence of CV disease was exceptionally low among these people. A Canadian study[5] looking at James Bay Cree people reported fewer CV risk factors and higher levels of plasma omega-3 fatty acids in adult Cree living along the coast than in those living inland (level II evidence).

In September 1989, the Diet and Reinfarction Trial (DART)[6] (level II evidence) was the first study to show that subjects who followed advice to eat fatty fish (high in omega-3 fatty acids) had a 29% reduction in 2-year all-cause mortality (P<.05). The study allocated 2033 men to 3 groups: group 1 reduced their fat intake and increased their intake of PUFA, group 2 increased their

fatty fish intake, and group 3 increased their cereal fibre intake.

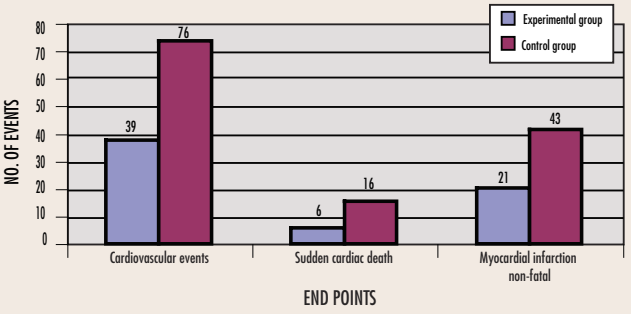
The Lyon Diet Heart Study,[7] a secondary prevention trial (level I evidence), followed 605 men after myocardial infarction (MI) for 4 years. One group (n=303) received a diet rich in omega-3 and omega-9 fatty acids and low in both omega-6 fatty acids and saturated fats (the Mediterranean diet). The second group (n=302) followed the Prudent Heart Diet, which is similar to the American Heart Association diet. Three end points were used: cardiac death or non-fatal MI; cardiac death or non-fatal MI plus secondary end points including unstable angina, stroke, heart failure, and pulmonary or peripheral embolism; and all of the preceding plus minor events requiring hospital admission. The experimental group following the Mediterranean diet had fewer events at all end points. For the first end point, the first group had 14 events, and the second group 44 events ($P<.0002$). For the second end point, the first group had 27 events, and the second group had 90 events ($P<.0002$). For the third end point, the first group had 95 events, and the second group had 180 events ($P<.0002$)[34] (**Figure 1**[7]). The control group had an omega-6–to–omega-3 ratio of 10:1; the experimental group had a ratio of 4:1. A striking protective effect was reported with a 50% to 70% reduction in risk of recurrence of CV events after 4 years' follow up.

Figure 1. Data from the final report of the Lyon Diet Health Study[7]



In the Indo-Mediterranean Diet Heart Study (1000 patients)[8] (level I evidence), those in the experimental group (diet high in ALA) had fewer CV events than those in the control group (39 vs 76, $P<.001$). Also reduced were sudden cardiac death (6 vs 16, $P<.015$) and non-fatal MI (21 vs 43, $P<.001$) (**Figure 2**[7,34]). Omega-6–to–omega-3 ratios were 38:1 before the trial and 33:1 before the intervention; after 2 years in the trial, ratios were 9:1 in the experimental group and 21:1 among controls. The prevalence of coronary artery disease was 2% to 3% in rural areas of India and 9% to 14% in urban populations.

Figure 2. Data from the Indo-Mediterranean Diet Heart Study[7,34]



The high incidence in urban areas is thought to be due to intake of Indian ghee or clarified butter (rich in cholesterol oxides) and high omega-6–to–omega-3 ratios.[35,36]

The GISSI-Prevenzione trial (level I evidence)[9,10] randomly assigned 11 324 patients surviving a recent MI into 4 groups: one took a capsule containing 850 mg/d of omega-3 fatty acids each day, another took 300 IU of vitamin E daily, a third group took both each day, and the control group took nothing. After 3.5 years, overall mortality was reduced by 20% and CV mortality was reduced by 30% in the group taking capsules of omega-3 fatty acids. No benefit was apparent from taking vitamin E alone. A 45% reduction in sudden cardiac death ($P=.01$) accounted for most of the benefit. Omega-3 fatty acids seem to be able to stabilize contractile heart cells electrically and thus prevent ventricular arrhythmias.[23]

A meta-analysis by Bucher et al[11] (level I evidence) identified 11 trials published between 1966 and 1999 with a total of 7951 patients in intervention groups and 7855 in control groups. They found that intake of fish or fish oil reduced rates of overall mortality ($P<.001$), fatal MI ($P<.001$), and sudden cardiac death ($P<.01$). Mortality from coronary artery disease was reduced by 40% to 60% with consumption of 40 to 60 g of fish daily.

Several studies, including the Cardiovascular Health Study,[37] the Family Heart Study,[38] the Health Professionals Follow-up Study,[39] the Multiple Risk Factor Intervention Trial,[40] and the Nurses' Health Study,[41] showed benefit of ALA in CV disease. The Zutphen Elderly Study,[42] however, found a modest link between ALA and increased risk of CV disease. Excessive consumption of trans fatty acids might have contributed to this.

Although most studies have shown that omega-3 fatty acids are useful for secondary prevention of CV disease, some have shown no statistical benefit. A study done by Nilsen et al[12] (level I evidence) showed no benefit for prevention of further cardiac events in 300 patients from Norway. Those patients had significantly lower triglyceride levels ($P<.0001$) and significantly higher HDL levels ($P<.0016$) than most people. It is thought that no further benefit was possible among these people who already

consumed a great deal of fish in their diet. This study was also shorter than many of the studies listed above.

Severe familial hypertriglyceridemia

Supplementation with omega-3 fatty acids has been shown to be of benefit in severe familial hypertriglyceridemia. Richter et al[13] (level II evidence) demonstrated that adding 4.32 g/d of omega-3 fatty acids to the diet for 8 weeks reduced serum triglycerides from 18.29 to 10.1 mmol/L. Pschierer et al[14] (level II evidence) showed that serum triglycerides had decreased significantly from 16.9 to 11.2 mmol/L after 1 month, and further decreased after 11 months to 10.1 mmol/L on average with supplementation with omega-3 fatty acids.

Fish oil and HMG-CoA reductase inhibitors

The effectiveness of statins can be improved by adding omega-3 fatty acids to the diet.[43,44] A small study looked at combining statins and fish oil (level II evidence).[15] Adding 900 to 1800 mg of EPA to the diet of patients already taking HMG-CoA reductase inhibitors resulted in a further decrease in total cholesterol from 5.63 to 5.02 mmol/L ($P<.05$) and in triglycerides from 2.07 to 1.08 mmol/L ($P<.01$). Serum HDL increased significantly from 1.23 to 1.34 mmol/L ($P<.01$).

Cardiovascular surgery

In a study done by Eritsland et al[16] (level I evidence), 610 patients who underwent coronary artery bypass grafting were assigned to a fish-oil group (4 g/d of fish oil) or to a control group. The end point was patency of the graft at 1 year. A year later, vein graft occlusion was 27% in the experimental group and 33% in the control group ($P=.034$). Vein graft occlusion was inversely related to the relative change in serum omega-3 fatty acid levels. Initial studies done on coronary angioplasty patients[45] showed that fish oil had promise for reducing recurring stenosis, but later studies using higher doses did not show any statistically significant reduction.[46]

Dietary suggestions, discussion, and recommendations

In 1990, Canada was the first country to provide separate dietary recommendations for omega-6 and omega-3 fatty acids for people of all ages.[47] For adults between 25 and 49 years old, Health Canada suggests 1500 mg of omega-3 and 9000 mg of omega-6 polyunsaturates daily for men and 1100 mg of omega-3 and 7000 mg of omega-6 fatty acids daily for women. This results in an omega-6–to–omega-3 ratio of 6:1. It is thought that most Canadians do not have this modest daily intake of omega-3 fatty acids. Dietary sources of omega-3 fatty acids and some instructions for making them palatable are shown in **Table 3**.[48] Side effects and interactions associated with consumption of fish oil are listed in **Table 4**.[49-53]

Table 3. Sources of omega-3 essential fatty acids: *To consume the minimum daily amount of 1200 mg of omega-3 fatty acids, people can choose a variety of food from the list in this table or take 3-4 fish oil capsules daily.*

SOURCES OF OMEGA-3 FATTY ACIDS*	CONTENT OF EPA, DHA, OR ALA IN THESE SOURCES	SOURCE OF EPA, DHA, OR ALA
Flax seed	2.2 g/5 mL	ALA
Flax oil†	8.5 g/5 mL	ALA
Purslane	Small amounts	ALA
Hemp oil†	3.1 g/5 mL	ALA
Canola oil	1.3 g/5 mL	ALA
Soya bean oil	0.9 g/5 mL	ALA
Dark green leafy vegetables	Small amounts	ALA
Walnuts and pine nuts	0.7 g/5 mL	ALA
Designer milk products		
• Beatrice omega-3 milk	0.3 g/250 mL	ALA
• Astro BioBest omega-3 yogurt	0.3 g/113 mL	ALA
• Lactantia Healthy Attitude omega-3 margarine	0.5 g/10 g	ALA
• Black Diamond DHA omega-3 natural cheese	0.1 g/30 g	DHA
Krill oil (omega-3–to–omega-6 ratio is 13:16) and other shellfish	Varies	DHA, EPA
Fish		
• Sockeye and chum salmon	1 g/130 g	DHA, EPA
• Chinook salmon	1 g/60 g	DHA, EPA
• Rainbow trout	1 g/90-95 g	DHA, EPA
• Mackerel	1 g/60-240 g	DHA, EPA
• Sardines	1 g/60-85 g	DHA, EPA
• Herring	1 g/30-60 g	DHA, EPA
Other seafood	Varies	DHA, EPA
Cod-liver oil‡	1 g/5 mL	DHA, EPA
Fish oil§	1 g/3 mL	DHA, EPA
Designer eggs		
• Omega-3 egg‖	1 g/2.5 eggs	DHA, EPA
• Dr Sims egg¶	1 g/1.6 eggs	DHA, EPA
Omacor capsule (not currently available)	850 mg	DHA, EPA

ALA—alpha-linolenic acid, DHA—docosahexaenoic acid, EPA—eicosapentenoic acid.
*Includes long-chain polyunsaturated fatty acids, EPA and DHA, and plant-source omega-3 fatty acid, ALA.
†Flax oil and hemp oil can be mixed into salad dressings and other food. These oils oxidize easily and should never be used for cooking.
‡Also a good source of vitamins A and D.
§Fish-oil flavours are milder in capsules, especially if capsules are swallowed cold from the refrigerator.
‖Each designer omega-3 egg has 0.38 g of DHA and EPA (omega-6–to–omega-3 ratio is 1.6:1), 7 times as much vitamin E as, and less cholesterol than, a normal egg.
¶ A Dr Sims designer egg has 0.6 g of DHA and EPA (omega-6–to–omega-3 ratio is 1:1). A normal egg has 0.05 g of DHA and EPA.
Data from Kris-Etherton et al.[48]

Table 4. Fish-oil interactions and side effects

INTERACTIONS AND SIDE EFFECTS	CONCERNS
INTERACTIONS	
Coumadin	Increased bleeding time[49]
Digoxin	Increased response to digitalis[50]
SIDE EFFECTS	
High doses (>15 g) of fish oil	Increased bleeding time[51]
Flax and flax oil	Rare allergy reported[52]
Fish oil	Fishy taste and belching of fishy flavours
Oily fish	Mercury and dioxins in larger fish, especially shark or swordfish. Fish oil has been shown to have less mercury[53]

The American Heart Association issued new recommendations on consumption of omega-3 fatty acids in 2003.[48] These are listed in **Table 5**[48,54] along with recommendations from an expert round-table discussion at the 34th Annual Scientific Meeting of the European Society for Clinical Investigation.[54]

Conclusion

There is now solid evidence that omega-3 fatty acids favourably modulate disease processes, such as hypertension, coronary artery disease, and hypertriglyceridemia. Increasing dietary intake of omega-3 fatty acids and bringing the ratio of omega-3 to omega-6 fatty acids into a healthy balance would improve Canadians' cardiovascular health.

Competing interests

None declared

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References

1. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens* 2002;20(8):1493-9.
2. Appel LJ, Miller ER III, Seidler AJ, Whelton PK. Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med* 1993;153(12):1429-38.
3. Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. *Acta Med Scand* 1972;192(1-2):85-94.
4. Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr* 1975;28(9):958-66.
5. Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ. Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. *Am J Clin Nutr* 2002;76(1):85-92.
6. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757-61.
7. Leaf A. Dietary prevention of coronary heart disease: the Lyon Diet Heart Study. *Circulation* 1999;99(6):733-5.
8. Singh RB, Dubnov G, Niaz MJ, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. *Lancet* 2002;360(9344):1455-61.
9. Stone NJ. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)-Prevenzione Trial on fish oil and vitamin E supplementation in myocardial infarction survivors. *Curr Cardiol Rep* 2000;2(5):445-51.

Table 5. Recommendations of the American Heart Association[48] and the European Society for Clinical Investigation[54] regarding consumption of omega-3 fatty acids

PATIENTS' CONDITIONS	AMERICAN HEART ASSOCIATION[48]	EUROPEAN SOCIETY FOR CLINICAL INVESTIGATION[54]
No documented coronary artery disease	Eat a variety of oily fish* at least twice weekly Include oils and foods rich in ALA (1.5-3.0 g) daily	Reduce coronary artery disease mortality by consuming 1-2 fish meals weekly Reduce risk of myocardial infarction with 1% of energy supplied by plant-based (ALA) omega-3 fatty acids
Documented coronary artery disease	Consume 1 g of EPA and DHA derived from oily fish daily Supplements can be considered Consume foods rich in ALA as well	Reduce risk of total, cardiovascular, coronary artery, and sudden death mortality after myocardial infarction by treating with 1 g/d of omega-3 fatty acids, mainly EPA and DHA, irrespective of high or low consumption of fish
Hyper-triglyceridemia	Consume 2-4 g of EPA and DHA daily under a doctor's supervision	Reduce coronary risk profile in patients with dyslipidemia with 1-4 g/d of omega-3 fatty acids of marine origin. A potent alternative is to combine statins with marine omega-3 fatty acids
Hypertension	Dose-dependent response to EPA and DHA; however, difficult to maintain supplementation with >4 g/d to achieve maximum benefit	Reduce moderate hypertension with 4 g/d of omega-3 fatty acids of marine origin Protect against development of hypertension in heart transplant patients with 4 g/d of omega-3 fatty acids of marine origin
Coronary artery bypass grafting	No recommendations	Reduce graft occlusion rates with 4 g/d of omega-3 fatty acids of marine origin
Coronary angioplasty	Omega-3 fatty acids not recommended	Omega-3 fatty acids not recommended

ALA—alpha-linolenic acid, DHA—docosahexaenoic acid, EPA—eicosapentenoic acid.
*Lean fish have smaller amounts of omega-3 fatty acids; fried fish (frozen breaded fish products or fish from fast-food outlets) have minimal amounts of omega-3 fatty acids

10. Marchioli R, Schweiger C, Tavazzi L, Valagussa F. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lipids* 2001;36(Suppl):S119-26.
11. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002;112(4):298-304.
12. Nilsen DW, Albreksten G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001;74(1):50-6.
13. Richter WO, Jacob BG, Ritter MM, Schwandt P. Treatment of primary chylomicronemia due to familial hypertriglyceridemia by omega-3 fatty acids. *Metabolism* 1992;41(10):1100-5.
14. Pschierer V, Richter WO, Schwandt P. Primary chylomicronemia in patients with severe familial hypertriglyceridemia responds to long-term treatment with (n-3) fatty acids. *J Nutr* 1995;125(6):1490-4.
15. Nakamura N, Ohta M, Okuda K, Urakazi M, Sawazaki S, Yamazaki K, et al. Joint effects of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile and plasma fatty acid concentrations in patients with hyperlipidemia. *Int J Clin Lab Res* 1999;29(1):22-5.
16. Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 1996;77(1):31-6.
17. Lichtenstein AH, Kennedy E, Barrier P, Danford D, Ernst ND, Grundy SM, et al. Dietary fat consumption and health. *Nutr Rev* 1998;56(5 Pt 2):S3-19; discussion S19-28.
18. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother* 2002;56(8):365-79.
19. Connor WE. Importance of n-3 fatty acids in health and disease. *Am J Clin Nutr* 2000;71(1 Suppl):171-5S.
20. Simopoulos AP. Human requirement for N-3 polyunsaturated fatty acids. *Poult Sci* 2000;79(7):961-70.
21. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54(3):438-63.
22. De Gomez Dumm IN, Brenner RR. Oxidative desaturation of alpha-linoleic, linoleic, and stearic acids by human liver microsomes. *Lipids* 1975;10(6):315-7.
23. Rosenberg IH. Fish—food to calm the heart. *N Engl J Med* 2002;346(15):1102-3.
24. Harris WS. Are omega-3 fatty acids the most important nutritional modulators of coronary heart disease risk? *Curr Atheroscler Rep* 2004;6(6):447-52.
25. Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J. Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease. *Arterioscler Thromb Vasc Biol* 1997;17(2):279-86.
26. Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003;361(9356):477-85.
27. Heller A, Koch T. Schmeck K, van Ackem K. Lipid mediators in inflammatory disorders. *Drugs* 1998;55(4):487-96.
28. Zhao G, Etherton TD, Martin KR, West SG, Gillies PJ, Kris-Etherton PM. Dietary alpha-linolenic acid reduces inflammatory and lipid cardiovascular risk factors in hypercholesterolemic men and women. *J Nutr* 2004;134(11):2991-7.
29. Fleischhauer FJ, Yan WD, Fischell TA. Fish oil improves endothelium-dependent coronary vasodilation in heart transplant recipients. *J Am Coll Cardiol* 1993;21(4):982-9.
30. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. *J Lipid Res* 1989;30(6):785-807.
31. Calabresi L, Villa N, Canavesi M, Sirtori CR, James RW, Bernini F, et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. *Metabolism* 2004;53(2):153-8.
32. Herrmann W, Biermann J, Kostner GM. Comparison of effects of N-3 to N-6 fatty acids on serum level of lipoprotein(a) in patients with coronary artery disease. *Am J Cardiol* 1995;76(7):459-62.
33. Din JN, Newby DE, Flapan AD. Omega 3 fatty acids and cardiovascular disease—fishing for a natural treatment. *BMJ* 2004;328(7430):30-5.
34. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99(6):779-85.
35. Pella D, Dubnov G, Singh RB, Sharma R, Berry EM, Manor O. Effects of an Indo-Mediterranean diet on the omega-6/omega-3 ratio in patients at high risk of coronary artery disease: the Indian paradox. *World Rev Nutr Diet* 2003;92:74-80.
36. Jacobson MS. Cholesterol oxides in Indian ghee: possible cause of unexplained high risk of atherosclerosis in Indian immigrant populations. *Lancet* 1987;2(8560):656-8.
37. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003;77(2):319-25.
38. Djousse L, Folsom AR, Province MA, Hunt SC, Ellison RC; National Heart, Lung, and Blood Institute Family Heart Study. Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Clin Nutr* 2003;77(4):819-25.
39. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ* 1996;313(7049):84-90.
40. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial. *Proc Soc Exp Biol Med* 1992;200(2):177-82.
41. Hu FB, Stampfer MA, Manson JE, Rimm EB, Wolk A, Colditz GA, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr* 1999;69(5):890-7.
42. Oomen CM, Ocke MC, Feskens EJ, Kok FJ, Kromhout D. Alpha-Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am J Clin Nutr* 2001;74(4):457-63.
43. Das UN. Essential fatty acids as possible mediators of the actions of statins. *Prostaglandins Leukot Essent Fatty Acids* 2001;65(1):37-40.
44. Nakamura N, Hamazaki T, Jokaji H, Minami S, Kobayashi M. Effect of HMG-CoA reductase inhibitors on plasma polyunsaturated fatty acid concentrations in patients with hyperlipidemia. *Int J Clin Lab Res* 1998;28(3):192-5.

EDITOR'S KEY POINTS

- Historically, the human diet was high in omega-3 fatty acids. The ratio of omega-6 to omega-3 fatty acids in the diet was 1-2:1. During the last 100 years, there has been a marked increase in consumption of omega-6 and a decrease in consumption of omega-3 fatty acids.
- There appears to be good evidence (level I and II) of a lower incidence of hypertension, cardiac disease, all-cause mortality, and familial hypertriglyceridemia in patients who consume adequate amounts of omega-3 fatty acids.
- Canada was the first country to adopt guidelines to reduce consumption of omega-6 and increase consumption of omega-3 fatty acids, with a target ratio of 6:1 in the diet. Most Canadians will not achieve this goal.
- Family doctors can be confident that promoting a diet with increased intake of omega-3 fatty acids is an important preventive measure.

POINTS DE REPÈRE DU RÉDACTEUR

- Historiquement, l'alimentation humaine contenait beaucoup d'acides gras oméga-3 et il y avait un rapport de 1-2:1 entre les oméga-6 et les oméga-3 consommés. Au cours des 100 dernières années, la consommation des oméga-6 a fortement augmenté tandis que celle des oméga-3 diminuait.
- Il y a des preuves de niveau I et II suggérant que la consommation d'une quantité adéquate d'acides gras oméga-3 réduit la mortalité globale et l'incidence d'hypertension, de maladies cardiaques et d'hypertriglycéridémie familiale.
- Le Canada a été le premier pays à adopter des directives pour réduire la consommation des oméga-6 et augmenter celle des oméga-3, avec comme objectif un rapport de 6:1 dans l'alimentation. La plupart des canadiens n'atteindront toutefois pas cet objectif.
- Le médecin de famille a raison de croire que le fait de préconiser un régime plus riche en oméga-3 est une importante mesure préventive.

45. Dehmer GJ, Popma JJ, van den Berg EK, Eichhom EJ, Prewitt JB, Campbell WB, et al. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. *N Engl J Med* 1988;319(12):733-40.
46. Johansen O, Brekke M, Seljeflot I, Abdelnoor M, Arnesen H. N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial. *J Am Coll Cardiol* 1999;33(6):1619-26.
47. Scientific Review Committee. *Nutritional recommendations.* (Document H49-42/1990E). Ottawa, Ont: National Health and Welfare Canada; 1990.
48. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2003;23(2):e20-30.
49. Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. *Ann Pharmacother* 2004;38(1):50-2.
50. Bernard M, Gerbi A, Barbey O, Jamme I, Cozzone PJ, Maixent JM. Dietary fish oil promotes positive inotropy and efficiency of digitalis. *Lipids* 1999;34(Suppl):S195.
51. Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis* 1995;6(1):17-22.
52. Lezaun A, Fraj J, Colas C, Duce F, Dominguez MA, Cuevas M, et al. Anaphylaxis from linseed. *Allergy* 1998;53(1):105-6.
53. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med* 2003;127(12):1603-5.
54. Nordoy A, Marchioli R, Arnesen H, Videbaek J. n-3 polyunsaturated fatty acids and cardiovascular diseases. *Lipids* 2001;36(Suppl):S127-9.