Fish Oil and CVD

Am J Cardiol. 2006 Apr 15;97(8):1127-1130. Epub 2006 Mar 3.

Effects of Omega-3 Fatty Acids on Resting Heart Rate, Heart Rate Recovery After Exercise, and Heart Rate Variability in Men With Healed Myocardial Infarctions and Depressed Ejection Fractions.

O'keefe JH Jr, Abuissa H, Sastre A, Steinhaus DM, Harris WS

We explored possible mechanisms by which recommended intakes of omega-3 fatty acids may decrease the risk for sudden cardiac death in patients with documented coronary heart disease. The cardioprotective effects of omega-3 fatty acids have been documented in epidemiologic and randomized controlled trials. These fatty acids are presumed to decrease susceptibility to fatal arrhythmias, but whether this is mediated by classic risk factors or direct cardiac mechanisms is not known. Eighteen white men with a history of myocardial infarction and ejection fractions <40% were randomized to placebo or omega-3 fatty acids (585 mg of docosahexaenoic acid and 225 mg of eicosapentaenoic acid) for two 4-month periods in a crossover design. At the end of each period, heart rate (HR), HR variability, and rate of HR recovery after exercise were determined, as were effects on arterial compliance, blood pressure, cardiac function, and fasting serum levels of lipids and inflammatory markers. Omega-3 fatty acids decreased HR at rest from 73 +/- 13 to 68 +/- 13 beats/min ($p < 0.0001$) and improved 1-minute HR recovery after exercise (-27 +/- 10 to -32 +/- 12 beats/min, $p < 0.01$). HR variability in the high-frequency band increased ($p < 0.02$), but no change was noted in overall HR variability. There were no significant effects on blood pressure, arterial compliance, lipids, or inflammatory markers. These changes are consistent with an increase in vagal activity and may in part explain the observed decrease in risk for sudden cardiac death seen with omega-3 fatty acid supplementation.

BMJ. 2006 Apr 1;332(7544):752-60. Epub 2006 Mar 24.

Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, Durrington PN, Higgins JP, Capps NE, Riemersma RA, Ebrahim SB, Davey Smith G.

OBJECTIVE: To review systematically the evidence for an effect of long chain and shorter chain omega 3 fatty acids on total mortality, cardiovascular events, and cancer. DATA SOURCES: Electronic databases searched to February 2002; authors contacted and bibliographies of randomised controlled trials (RCTs) checked to locate studies. REVIEW METHODS: Review of RCTs of omega 3 intake for (3) 6 months in adults (with or without risk factors for cardiovascular disease) with data on a relevant outcome. Cohort studies that estimated omega 3 intake and related this to clinical outcome during at least 6 months were also included. Application of inclusion criteria, data extraction, and quality assessments were performed independently in duplicate. RESULTS: Of 15,159 titles and abstracts assessed, 48 RCTs (36,913 participants) and 41 cohort studies were analysed. The trial results were inconsistent. The pooled estimate showed no strong evidence of reduced risk of total mortality (relative risk 0.87, 95% confidence interval 0.73 to 1.03) or combined cardiovascular events (0.95, 0.82 to 1.12) in participants taking additional omega 3 fats. The few studies at low risk of bias were more consistent, but they showed no effect of omega 3 on total mortality (0.98, 0.70 to 1.36) or cardiovascular events (1.09, 0.87 to 1.37). When data from the subgroup of studies of long chain omega 3 fats were analysed separately, total mortality (0.86, 0.70 to 1.04; 138 events) and cardiovascular events (0.93, 0.79 to 1.11) were not clearly reduced. Neither RCTs nor cohort studies suggested increased risk of cancer with a higher intake of omega 3 (trials: 1.07, 0.88 to 1.30; cohort studies: 1.02, 0.87 to 1.19), but clinically important harm could not be excluded. CONCLUSION: Long chain and shorter chain omega 3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer.

Int J Obes (Lond). 2006 Mar 21; [Epub ahead of print]

Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women.

Krebs JD, Browning LM, McLean NK, Rothwell JL, Mishra GD, Moore CS, Jebb SA.

Background:Obesity, inflammation, insulin resistance and cardiovascular disease (CVD) risk are inter-related. Both weight-loss and long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) are independently known to reduce metabolic risk, but the combined effects are unclear.Objective:This study examines whether addition of LC n-3 PUFA to a low fat/high carbohydrate weight-loss programme results in greater improvements in inflammation, insulin sensitivity and CVD risk, than weight-loss alone.Design:One hundred and sixteen overweight insulin-resistant women entered a 24-week randomised intervention study. Thirty-nine women were randomised to a weight-loss programme, with LC n-3 PUFA (WLFO), 38 to a weight-loss programme with placebo oil (WLPO), and 39 to receive placebo oil, with no weight-loss programme (control).Results:Ninety-three women completed the study (35 WLFO, 32 WLPO and 26 control), with significant weight-loss in WLFO (10.8+/-1.0%) and WLPO (12.4+/-1.0%) compared to the control group (P<0.0001). The WLFO, but not WLPO or control group, showed significant increases in adipose tissue LC n-3 PUFA (0.34+/-0.20 vs 0.17+/-0.10 and 0.16+/-0.10 %DHA, P<0.0001). Weight-loss showed significant improvements in insulin sensitivity (P<0.001), lipid profile (triglycerides P<0.05) and inflammation (sialic acid P<0.05). Time*group effects showed significant decreases in triglycerides (P<0.05) and increases in adiponectin (P<0.01) with LC n-3 PUFA, in the WLFO vs WLPO groups.Conclusions:Weight-loss improved risk factors associated with CVD, with some additional benefits of LC n-3 PUFA on triglycerides and adiponectin. Given the current low dietary intake of LC n-3 PUFA, greater attention should be given to increase these fatty acids in the treatment of obesity.International Journal of Obesity advance online publication, 21 March 2006; doi:10.1038/sj.ijo.0803309.

Atherosclerosis. 2006 Mar 9; [Epub ahead of print]

Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J.

Greater fish oil consumption has been associated with reduced CVD risk, although the mechanisms are unclear. Plant-source oil omega-3 fatty acids (ALA) have also been studied regarding their cardiovascular effect. We conducted a systematic review of randomized controlled trials that evaluated the effect of consumption of fish oil and ALA on commonly measured serum CVD risk factors, performing meta-analyses when appropriate. Combining 21 trials evaluating lipid outcomes, fish oil consumption resulted in a summary net change in triglycerides of -27 (95% CI -33, -20)mg/dL, in HDL cholesterol of +1.6 (95% CI +0.8, +2.3)mg/dL, and in LDL cholesterol of +6 (95% CI +3, +8)mg/dL. There was no effect of fish oil on total cholesterol. Across studies, higher fish oil dose and higher baseline levels were associated with greater reductions in serum triglycerides. Overall, the 27 fish oil trials evaluating Hgb A(1c) or FBS found small non-significant net increases compared to control oils. Five studies of ALA were inconsistent in their effects on lipids, Hgb A(1c) or FBS. Four studies investigating the effects of omega-3 fatty acids on hs-CRP were also inconsistent and non-significant. The evidence supports a dose-dependent beneficial effect of fish oil on serum triglycerides, particularly among people with more elevated levels. Fish oil consumption also modestly improves HDL cholesterol, increases LDL cholesterol levels, but does not appear to adversely affect glucose homeostasis. The evidence regarding the effects of omega-3 fatty acids on hs-CRP is inconclusive, as are data on ALA.

Curr Opin Clin Nutr Metab Care. 2006 Mar;9(2):95-104.

The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans.

Mori TA, Woodman RJ.

PURPOSE OF REVIEW: This review details the independent effects of purified eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. We report data from the recent literature and our own controlled clinical trials which compared the independent effects of these fatty acids in individuals at increased risk of cardiovascular disease, namely overweight hyperlipidaemic men and treated-hypertensive, type 2 diabetic men and women. We discuss the biological effects of these fatty acids and the potential mechanisms through which they may affect cardiovascular disease risk factors. RECENT FINDINGS: A cardioprotective effect for omega3 fatty acids is supported by prospective studies demonstrating an inverse association between fish intake and coronary heart disease mortality. Data from secondary prevention trials support a reduction in ventricular fibrillation as a primary mechanism for the decreased incidence of myocardial infarction. Clinical trials and experimental studies have shown that omega3 fatty acids have many other potentially important antiatherogenic and antithrombotic effects. Omega-3 fatty acids lower blood pressure and heart rate, improve dyslipidaemia, reduce inflammation, and improve vascular and platelet function. These favourable effects have until recently been primarily attributed to the omega3 fatty acid eicosapentaenoic acid, which is present in large amounts in fish oil. Controlled studies in humans now demonstrate that docosahexaenoic acid, although often present in lower quantities, has equally important anti-arrhythmic,

anti-thrombotic and anti-atherogenic effects. SUMMARY: Available evidence strongly suggests that eicosapentaenoic acid and docosahexaenoic acid have differing haemodynamic and anti-atherogenic properties. The effects of the two fatty acids may also differ depending on the target population.

Prog Biophys Mol Biol. 2006 Jan-Apr;90(1-3):299-325. Epub 2005 Jun 15.

Dietary long-chain omega-3 fatty acids of marine origin: a comparison of their protective effects on coronary heart disease and breast cancers.

Jude S, Roger S, Martel E, Besson P, Richard S, Bougnoux P, Champeroux P, Le Guennec JY.

The relationship between high fish consumption and low mortality following coronary heart disease (CHD) and low incidence of breast cancer was first mentioned 3 decades ago. The fishes of interest are rich in omega-3 long-chain polyunsaturated fatty acids (omega-3 LC-PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which could be the active nutrients. The current consensus about cardioprotection is that omega-3 LC-PUFAs would mainly exert antiarrhythmic effects. One of the proposed mechanisms is that circulating non-esterified LC-PUFAs partition into cardiac cells membrane phospholipids and exert a direct effect on ionic channels and/or modify intracellular calcium homeostasis. In another hypothesis, changes in the metabolism of phosphoinositides would be involved and lead to the differential activation of PKC isoforms. As compared to the mechanisms proposed for the cardioprotective effects of omega-3 LC-PUFAs, less is known about the molecular mechanisms involved in breast cancers prevention. Some proposed mechanisms such as the modulation of phosphoinositides metabolism and/or modulation of intracellular calcium homeostasis, are common to both pathologies. Other hypotheses involve the alteration of the cellular redox status induced by highly peroxidizable polyunsaturated fatty acids (FA), or the modulation of gene expression, both phenomena being tightly linked to apoptosis. In this review, we report and compare some proposed mechanisms for the involvement of omega-3 LC-PUFAs in both cardiac and breast cancer protection. Deliberately, we chose to discuss only the mechanisms, which are less described in other reviews such as ionic channels in cancer, calcium homeostasis, PKC activation or matrix metalloproteinases in both cancer and cardiac models. The leitmotiv along this review is that cardio- and cancero-protective effects use common pathways. Comparison of the cellular effects might therefore help to highlight the "protective" pathways.

J Cardiovasc Nurs. 2006 Jan-Feb;21(1):17-24, quiz 25-6.

Omega-3 fatty acids: role in cardiovascular health and disease.

Engler MM, Engler MB.

Dietary omega-3 polyunsaturated fatty acids, eicosapentaenoic and docosahexaenoic acids, play an important role in cardiovascular health and disease. Clinical trials provide substantial evidence to support current dietary recommendations for omega-3 fatty acids in cardiovascular disease management. The cardioprotective benefits of omega-3 fatty acids may be attributed to multiple physiological effects on lipids, blood pressure, vascular function, cardiac rhythms, platelet function, and inflammatory responses. The metabolism of omega-3 fatty acids, physiological effects, and clinical considerations with current dietary recommendations and sources of omega-3 fatty acids are presented.

Circulation. 2006 Jan 17;113(2):195-202. Epub 2006 Jan 9.

Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I.

Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group.

BACKGROUND: Once- or twice-weekly consumption of fish (or a small amount of fish intake) reduces the risk of coronary heart disease and sudden cardiac death in Western countries. It is uncertain whether a high frequency or large amount of fish intake, as is the case in Japan, further reduces the risk. METHODS AND RESULTS: To examine an association between high intake of fish and n3 polyunsaturated fatty acids and the risk of coronary heart disease, a total of 41,578 Japanese men and women aged 40 to 59 years who were free of prior diagnosis of cardiovascular disease and cancer and who completed a food frequency questionnaire were followed up from 1990-1992 to 2001. After 477,325 person-years of follow-up, 258 incident cases of coronary heart disease (198 definite and 23 probable myocardial infarctions and 37 sudden cardiac deaths) were documented, comprising 196 nonfatal and 62 fatal coronary events. The multivariable hazard ratios (HRs) and 95% confidence intervals in the highest (8 times per week, or median intake=180 g/d) versus lowest (once a week, or median intake=23 g/d) quintiles of fish intake were 0.63 (0.38 to 1.04) for total coronary heart disease, 0.44 (0.24 to 0.81) for definite myocardial infarction, and 1.14 (0.36 to 3.63) for sudden cardiac death. The reduced risk was primarily observed for nonfatal coronary events (HR=0.43 [0.23 to 0.81]) but not for fatal coronary events (HR=1.08 [0.42 to 2.76]). Strong inverse associations existed between dietary intake of n3 fatty acids and risk of definite myocardial infarction (HR=0.35 [0.18 to 0.66]) and nonfatal

coronary events (HR=0.33 [0.17 to 0.63]). CONCLUSIONS: Compared with a modest fish intake of once a week or &20 g/d, a higher intake was associated with substantially reduced risk of coronary heart disease, primarily nonfatal cardiac events, among middle-aged persons.

Am J Cardiol. 2005 Dec 1;96(11):1521-9. Epub 2005 Oct 21.

Usefulness of omega-3 fatty acids and the prevention of coronary heart disease.

Harper CR, Jacobson TA.

Clinical trial evidence exists that supports a role for the omega-3 polyunsaturated fatty acids in coronary heart disease prevention. However, the results from these clinical trials have varied and were conducted in diverse population groups using several different types of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid (ALA). Thus, we systematically reviewed previously published reports assessing the different types of omega-3 polyunsaturated fatty acid interventions and cardiovascular outcomes. Fourteen randomized clinical trials were included in the review. Six trials were included with fish oil, with 1 large trial (10,000 patients) dominating the analysis. In aggregate, the fish oil trials demonstrated a reduction in total mortality and sudden death without a clinically significant reduction in nonfatal myocardial infarction. The 6 trials with ALA supplements or an ALA-enriched diet were of poorer design than the fish oil trials and had limited power. Many of the trials with ALA involved other changes in dietary components. In aggregate, the ALA trials demonstrated possible benefits in reducing sudden death and nonfatal myocardial infarction, but with wider confidence intervals than in the fish oil trials. In conclusion, the evidence suggests a role for fish oil (eicosapentaenoic acid, docosahexaenoic acid) or fish in secondary prevention because recent clinical trial data have demonstrated a significant reduction in total mortality, coronary heart disease death, and sudden death. The data on ALA have been limited by studies of smaller sample size and limited quality.

Am J Prev Med. 2005 Nov;29(4):335-46.

A quantitative analysis of fish consumption and coronary heart disease mortality.

Konig A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM.

Although a rich source of n-3 polyunsaturated fatty acids (PUFAs) that may confer multiple health benefits, some fish contain methyl mercury (MeHg), which may harm the developing fetus. U.S. government recommendations for women of childbearing age are to modify consumption of high-MeHg fish to reduce MeHg exposure, while recommendations encourage fish consumption among the general population because of the nutritional benefits. The Harvard Center for Risk Analysis convened an expert panel (see acknowledgements) to quantify the net impact of resulting hypothetical changes in fish consumption across the population. This paper estimates the impact of fish consumption on coronary heart disease (CHD) mortality and nonfatal myocardial infarction (MI). Other papers quantify stroke risk and the impacts of both prenatal MeHg exposure and maternal intake of n-3 PUFAs on cognitive development. This analysis identified articles in a recent qualitative review appropriate for the development of a dose-response relationship. Studies had to satisfy quality criteria, quantify fish intake, and report the precision of the relative risk estimates. Relative risk results were averaged, weighted proportionately by precision. CHD risks associated with MeHg exposure were reviewed qualitatively because the available literature was judged inadequate for quantitative analysis. Eight studies were identified (29 exposure groups). Our analysis estimated that consuming small quantities of fish is associated with a 17% reduction in CHD mortality risk, with each additional serving per week associated with a further reduction in this risk of 3.9%. Small quantities of fish consumption were associated with risk reductions in nonfatal MI risk by 27%, but additional fish consumption conferred no incremental benefits.

Int J Circumpolar Health. 2005 Sep;64(4):387-95.

Eskimos have CHD despite high consumption of omega-3 fatty acids: the Alaska Siberia project.

Ebbesson SO, Risica PM, Ebbesson LO, Kennish JM.

OBJECTIVES: The thirty-year-old hypothesis that omega-3 fatty acid (FA) may "reduce the development of thrombosis and atherosclerosis in the Western World" still needs to be tested. Dyerberg-Bang based their supposition on casual observations that coronary atherosclerosis in Greenlandic Inuit was 'almost unknown' and that they consumed large amounts of omega-3 FAs. However, no association was demonstrated with data. STUDY DESIGN: Cross-sectional study. METHODS: 454 Alaskan Eskimos were screened for coronary heart disease (CHD), using a protocol that included ECG, medical history, Rose questionnaire, blood chemistries, including plasma FA concentrations, and a 24-hour recall and a food frequency questionnaire assessment of omega-3 FA consumption. RESULTS: CHD was found in 6% of the cohort under 55 years of age and in 26% of those > or = 55 years of age. Eskimos with CHD consume as much omega-3 FAs as those without CHD, and the plasma concentrations confirm that dietary assessment. CONCLUSIONS: Average daily consumption of omega-3 FAs among Eskimos was high, with about 3-4 g/d reported, compared with 1-2 g/d used in intervention studies and the average consumption of 0.2 g/d by the

American population. There was no association between current omega-3 FA consumption/blood concentrations and the presence of CHD.

Curr Atheroscler Rep. 2005 Sep;7(5):375-80.

Extending the cardiovascular benefits of omega-3 Fatty acids.

Harris WS.

The cardiovascular benefits of omega (n)-3 fatty acids (FA) become clearer with each passing year. Although useful in large doses for lowering serum triglyceride levels, the primary benefits are likely to arise from smaller, nutritional intakes of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA). Doses of less than 1 g/d appear to reduce risk for fatal coronary heart disease events, perhaps by stabilizing the myocardium and reducing risk for fatal arrhythmias. New evidence points to a possible benefit on atrial fibrillation, particularly in the immediate post-cardiac surgery setting. Studies in women with coronary heart disease now suggest that plaque progression may be slowed by increased intakes of oily fish, even in women with diabetes. The relative importance of the n-6 FA linoleic acid (LA), the short-chain n-3 FA alpha linolenic acid (ALA), and the long-chain n-3 FAs EPA and DHA is becoming clearer. If intakes of the latter are adequate (perhaps over 250 mg/d), then there appears to be little need to consume more ALA or less LA

J Membr Biol. 2005 Jul;206(2):103-16.

Omega-3 fatty acids and the regulation of expression of endothelial pro-atherogenic and pro-inflammatory genes.

De Caterina R, Massaro M.

By partially replacing the corresponding omega-6 analogues in membrane phospholipids, omega-3 fatty acids have been shown to decrease the transcriptional activation of genes--e.g., adhesion molecules, chemoattractants, inflammatory cytokines--involved in endothelial activation in response to inflammatory and pro-atherogenic stimuli. This regulation occurs, at least in part, through a decreased activation of the nuclear factor-kappaB system of transcription factors, secondary to decreased generation of intracellular hydrogen peroxide. Such regulation by omega-3 fatty acids is likely linked to the presence of a higher number of double bonds in the fatty acid chain in omega-3 compared with omega-6 fatty acids. By similar mechanisms, omega-3 fatty acids have been recently shown to reduce gene expression of cyclooxygenase-2, an inflammatory gene involved, through the activation of some metalloproteinases, in plaque angiogenesis and plaque rupture. The quenching of gene expression of pro-inflammatory pro-atherogenic genes by omega-3 fatty acids has consequences on the extent of leukocyte adhesion to vascular endothelium, early atherogenesis and later stages of plaque development and plaque rupture, ultimately yielding a plausible comprehensive explanation for the vasculoprotective effects of these nutrients.

Arterioscler Thromb Vasc Biol. 2005 Jan;25(1):228-33. Epub 2004 Nov 11.

Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland.

Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, Valkonen VP, Seppanen K, Laukkanen JA, Salonen JT.

OBJECTIVE: Mercury has been suggested to have negative effects on cardiovascular health. We investigated the effects of high mercury content in hair on the risk of acute coronary events and cardiovascular and all-cause mortality in men from eastern Finland. METHODS AND RESULTS: The population-based prospective Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) cohort of 1871 Finnish men aged 42 to 60 years and free of previous coronary heart disease (CHD) or stroke at baseline was used. During an average follow-up time of 13.9 years, 282 acute coronary events and 132 cardiovascular disease (CVD), 91 CHD, and 525 all-cause deaths occurred. Men in the highest third of hair mercury content (>2.03 microg/g) had an adjusted 1.60-fold (95% CI, 1.24 to 2.06) risk of acute coronary event, 1.68-fold (95% CI, 1.15 to 2.44) risk of CVD, 1.56-fold (95% CI, 0.99 to 2.46) risk of CHD, and 1.38-fold (95% CI, 1.15 to 1.66) risk of any death compared with men in the lower two thirds. High mercury content in hair also attenuated the protective effects of high-serum docosahexaenoic acid plus docosapentaenoic acid concentration. CONCLUSIONS: High content of mercury in hair may be a risk factor for acute coronary events and CVD, CHD, and all-cause mortality in middle-aged eastern Finnish men. Mercury may also attenuate the protective effects of fish on cardiovascular health.

Curr Med Res Opin. 2005 Jan;21(1):95-100.

The mechanism of action of omega-3 fatty acids in secondary prevention post-myocardial infarction.

Harrison N, Abhyankar B.

BACKGROUND: Omega-3 fatty acids from fish and fish oils can protect against coronary heart disease (CHD), which is still the most common cause of death in the Western economies. Evidence from epidemiological and case cohort studies indicate that consumpton of fatty fish and omega-3 fatty acids reduces the risk of cardiovascular mortality. OBJECTIVE:This article briefly reviews the evidence regarding omega-3 fatty acids and CHD and outlines the mechanisms through which omega-3 fatty acids might confer cardiac benefits over and above the standard secondary prevention strategies. CONCLUSION: The conclusion reached is that omega-3 fatty acids play a significant role in secondary prevention post-myocardial infarction. The mechanisms through which two of these omega-3 fatty acids, eicosapentaenoic acid and docosahexanoic acid, exert their action appear to be distinct and adjuvant to the available standard secondary prevention therapies. The role to be played by the administration of a newly licensed 90% concentrate EPA + DHA formulation (1 g/day capsule: Omacor) is explored.

Curr Atheroscler Rep. 2004 Nov;6(6):447-52.

Are omega-3 fatty acids the most important nutritional modulators of coronary heart disease risk?

Harris WS.

With each passing year, the evidence linking an increased risk for coronary heart disease (CHD) death with a chronic dietary deficiency in long-chain omega-3 (n-3) fatty acids (FAs) grows stronger. Recently, a federally mandated evidence-based review in the United States concluded that n-3 FAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have clear cardioprotective effects, and national and international expert panels and health organizations have begun to call for increased EPA and DHA intakes. Consumption of between 450 and 1000 mg/d is recommended for those without and with known CHD, respectively. Based on animal and isolated cell studies, these FAs were presumed to have antiarrhythmic effects. The first direct evidence for this in humans was recently published, as were new data linking low n-3 FA intakes with risk for developing atrial fibrillation. The strength of the n-3 story has now led to a proposal that blood levels of EPA plus DHA be considered a new, modifiable, and clinically relevant risk factor for death from CHD.

Am J Epidemiol. 2004 Nov 15;160(10):1005-10.

Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women.

Folsom AR, Demissie Z.

Intake of fish or omega-3 fatty acids may decrease risk of total and coronary heart disease death, but evidence from low-risk populations is less convincing. The authors assessed intake by using a food frequency questionnaire at baseline in a cohort of Iowa women aged 55-69 years. Among women initially free of heart disease and cancer (4,653 deaths over 442,965 person-years), there was an inverse age- and energy-adjusted association between total mortality and fish intake, with a relative risk of 0.82 (95% confidence interval: 0.74, 0.91) for the highest versus lowest quintile. Age- and energy-adjusted associations also were inverse (p for trend < 0.05), although not entirely monotonic, for cardiovascular, coronary heart disease, and cancer mortality. Adjustment for multiple other risk factors attenuated all associations to statistically nonsignificant levels. Estimated marine omega-3 fatty acid intake also was not associated with total or cause-specific mortality. In comparison, plant-derived alpha-linolenic acid was inversely associated with mortality after multivariable adjustment. Intake of neither fish nor marine omega-3 fatty acids was associated with breast cancer incidence. These findings do not argue against recommending fish as part of a healthy diet, as other evidence suggests benefit. Nevertheless, the authors of this 1986-2000 study could not verify that fish and marine omega-3 fatty acid intake had independent health benefits in these postmenopausal women.

Fundam Clin Pharmacol. 2004 Oct;18(5):581-92.

Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials.

Yzebe D, Lievre M.

What is the place of fish oils in the care of coronary heart disease (CHD) patients? As several clinical trials have already addressed this question without giving definitive answers, we did a meta-analysis of trials regarding the efficacy of omega-3 fatty acids in preventing cardiovascular mortality and morbidity. We searched the MEDLINE (1966-2003), EMBASE databases, proceedings abstracts and references of reviewed articles. Randomized controlled trials (RCTs) of the efficacy of omega-3 fatty acids among adults with recent or acute myocardial infarction (MI), or angina were selected. Two reviewers abstracted data

independently. Five relevant outcomes, mortality from all causes, fatal and non-fatal MI, non-fatal stroke and angina, were measured. Data were synthesized using a fixed effect model. Ten RCTs with 14,727 patients were included. No significant heterogeneity was detected. Daily intake of omega-3 fatty acids for a mean duration of 37 months decreased all causes of mortality by 16% (relative risk 0.84, 95% confidence interval [0.76; 0.94]) and the incidence of death due to MI by 24% (0.76, [0.66; 0.88]). No significant effect was found for the other outcomes. Because of the suboptimal quality of the studies included into the meta-analysis and the absence of data in patients receiving statins, these results do not justify adding fish oils systematically to the heavy pharmaceutical assortment already recommended in CHD patients.

Am J Clin Nutr. 2004 Sep;80(3):626-32.

Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease.

Erkkila AT, Lichtenstein AH, Mozaffarian D, Herrington DM.

BACKGROUND: Higher intakes of fish and n-3 fatty acids are associated with a reduced risk of cardiovascular events and mortality. However, limited data exist on the effect of fish intake on actual measures of progression of coronary artery atherosclerosis. OBJECTIVE: The aim was to examine the association between fish intake and the progression of coronary artery atherosclerosis in women with coronary artery disease. DESIGN: This was a prospective cohort study of postmenopausal women (n = 229) participating in the Estrogen Replacement and Atherosclerosis trial. Usual fish intake was estimated at baseline with a food-frequency questionnaire. Quantitative coronary angiography was performed at baseline and after 3.2 +/- 0.6 (x +/- SD) y to evaluate changes in the mean minimum coronary artery diameter, the mean percentage of stenosis, and the development of new coronary lesions. RESULTS: Compared with lower fish intakes, consumption of > or =2 servings of fish or > or =1 serving of tuna or dark fish per week was associated with smaller increases in the percentage of stenosis (4.54 +/- 1.37% compared with -0.06 +/- 1.59% and 5.12 +/- 1.48% compared with 0.35 +/- 1.47%, respectively; $P < 0.05$ for both) in diabetic women after adjustments for age, cardiovascular disease risk factors, and dietary intakes of fatty acids, cholesterol, fiber, and alcohol. These associations were not significant in nondiabetic women. Higher fish consumption was also associated with smaller decreases in minimum coronary artery diameter and fewer new lesions. CONCLUSIONS: Consumption of fish is associated with a significantly reduced progression of coronary artery atherosclerosis in women with coronary artery disease.

Mol Cell Biochem. 2004 Aug;263(1-2):217-25.

Omega-3 fatty acids from fish oils and cardiovascular disease.

Holub DJ, Holub BJ.

Fish and fish oils contain the omega-3 fatty acids known as eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA). Epidemiological studies have shown an inverse relation between the dietary consumption of fish containing EPA/DHA and mortality from coronary heart disease. These relationships have been substantiated from blood measures of omega-3 fatty acids including DHA as a physiological biomarker for omega-3 fatty acid status. Controlled intervention trials with fish oil supplements enriched in EPA/DHA have shown their potential to reduce mortality in post-myocardial infarction patients with a substantial reduction in the risk of sudden cardiac death. The cardioprotective effects of EPA/DHA are widespread, appear to act independently of blood cholesterol reduction, and are mediated by diverse mechanisms. Their overall effects include anti-arrhythmic, blood triglyceride-lowering, anti-thrombotic, anti-inflammatory, endothelial relaxation, plus others. Current dietary intakes of EPA/DHA in North America and elsewhere are well below those recommended by the American Heart Association for the management of patients with coronary heart disease.

Clin Sci (Lond). 2004 Jul;107(1):1-11.

n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored.

Calder PC.

Long chain n-3 PUFAs (polyunsaturated fatty acids) are found in fatty fish and in fish oils. Substantial evidence from epidemiological and case-control studies indicates that consumption of fish, fatty fish and long-chain n-3 PUFAs reduces the risk of cardiovascular mortality. Secondary prevention studies using long-chain n-3 PUFAs in patients post-myocardial infarction have shown a reduction in total and cardiovascular mortality, with an especially potent effect on sudden death. Long-chain n-3 PUFAs have been shown to decrease blood triacylglycerol (triglyceride) concentrations, to decrease production of chemoattractants, growth factors, adhesion molecules, inflammatory eicosanoids and inflammatory cytokines, to lower blood pressure, to increase nitric oxide production, endothelial relaxation and vascular compliance, to decrease thrombosis and cardiac arrhythmias and to increase heart rate variability. These mechanisms most likely explain the primary and secondary cardiovascular protection afforded by long-chain n-3 PUFA consumption. A recent study suggests that long-chain n-3 PUFAs might also act to stabilize advanced atherosclerotic plaques, perhaps through their anti-inflammatory effects. As a result of the robust evidence in their favour, a number of recommendations to increase intake of long-chain n-3 PUFAs have been made.

Eur J Clin Nutr. 2004 Jul;58(7):1062-70.

Effects of trans- and n-3 unsaturated fatty acids on cardiovascular risk markers in healthy males. An 8 weeks dietary intervention study.

Dyerberg J, Eskesen DC, Andersen PW, Astrup A, Buemann B, Christensen JH, Clausen P, Rasmussen BF, Schmidt EB, Tholstrup T, Toft E, Toubro S, Stender S.

BACKGROUND: Studies of long-term intake of industrially produced trans fatty acids (TFA) and n-3 polyunsaturated fatty acids (PUFA) suggest opposite effects on cardiovascular disease risk. Common mechanisms of action are probable. OBJECTIVE: To examine the effects on cardiovascular risk markers of dietary enrichment with TFA or n-3 PUFA. DESIGN: Randomized, double-blind, parallel intervention trial. SETTING: Department of Human Nutrition, The Royal Veterinary and Agricultural University. SUBJECTS: In all, 87 healthy males included, 79 completed. INTERVENTION: Subjects were randomly assigned to 8 weeks of a daily intake of 33 g of experimental fats from either partially hydrogenated soy oil containing 20 g of TFA, 12 g of fish oil with approximately 4 g of n-3 PUFA and 21 g of control fat, or 33 g of control fat. The experimental fats were incorporated into bakery products. Plasma lipids, blood pressure, heart rate variability (HRV), arterial dilatory capacity, compliance, and distensibility were recorded before and after intervention and at follow-up 12 weeks after the intervention. RESULTS: High-density lipoprotein cholesterol (HDL-C) decreased in the TFA group and triglycerides and mean arterial blood pressure decreased in the n-3 PUFA group compared to the control group. HRV, arterial dilatory capacity, compliance, and distensibility were unchanged. CONCLUSION: The results indicate that the association between coronary heart disease risk and intake of TFA and n-3 PUFA relates only modestly to changes in traditional risk markers. SPONSORSHIP: Danish Medical Research Council (Grant no. 22-01-0390), Center of Advanced Food Research (Copenhagen, Denmark) (Grant no. KVL-R-2001-107), the Danish Heart Association (Grant no. 99-2-3-45-22748), Novozymes (Bagsvaerd, Denmark), Aarhus Olie (Aarhus, Denmark), and from private sources. The experimental fats were provided by Pronova Biocare (Aalesund, Norway) and Aarhus Olie (Aarhus, Denmark).

Am Fam Physician. 2004 Jul 1;70(1):133-40.

Omega-3 fatty acids.

Covington MB.

Omega-3 fatty acids have been shown to significantly reduce the risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease. Fatty fish, such as salmon and tuna, and fish oil are rich sources of the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. Flaxseed, canola oil, and walnuts also are good dietary sources of omega-3 fatty acids. In addition to being antiarrhythmic, the omega-3 fatty acids are antithrombotic and anti-inflammatory. In contrast, omega-6 fatty acids, which are present in most seeds, vegetable oils, and meat, are prothrombotic and proinflammatory. Omega-3 fatty acids also are used to treat hyperlipidemia, hypertension, and rheumatoid arthritis. There are no significant drug interactions with omega-3 fatty acids. The American Heart Association recommends consumption of two servings of fish per week for persons with no history of coronary heart disease and at least one serving of fish daily for those with known coronary heart disease. Approximately 1 g per day of eicosapentaenoic acid plus docosahexaenoic acid is recommended for cardioprotection. Higher dosages of omega-3 fatty acids are required to reduce elevated triglyceride levels (2 to 4 g per day) and to reduce morning stiffness and the number of tender joints in patients with rheumatoid arthritis (at least 3 g per day). Modest decreases in blood pressure occur with significantly higher dosages of omega-3 fatty acids.

Annu Rev Nutr. 2004;24:597-615.

Dietary n-6 and n-3 fatty acid balance and cardiovascular health.

Wijendran V, Hayes KC.

Epidemiological and clinical studies have established that the n-6 fatty acid, linoleic acid (LA), and the n-3 fatty acids, linolenic acid (LNA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) collectively protect against coronary heart disease (CHD). LA is the major dietary fatty acid regulating low-density lipoprotein (LDL)-C metabolism by downregulating LDL-C production and enhancing its clearance. Further, the available mass of LA is a critical factor determining the hyperlipemic effects of other dietary fat components, such as saturated and trans fatty acids, as well as cholesterol. By contrast, n-3 fatty acids, especially EPA and DHA, are potent antiarryhthmic agents. EPA and DHA also improve vascular endothelial function and help lower blood pressure, platelet sensitivity, and the serum triglyceride level. The distinct functions of these two families make the balance between dietary n-6 and n-3 fatty acids an important consideration influencing cardiovascular health. Based on published literature describing practical dietary intakes, we suggest that consumption of ~6% en LA, 0.75% en LNA, and 0.25% en EPA + DHA represents adequate and achievable intakes for most healthy adults. This corresponds to an n-6/n-3 ratio of ~6:1. However, the absolute mass of essential fatty acids consumed, rather than their n-6/n-3 ratio, should be the first consideration when contemplating lifelong dietary habits affecting cardiovascular benefit from their intake.

Reprod Nutr Dev. 2004 May-Jun;44(3):283-8.

Use and misuse of dietary fatty acids for the prevention and treatment of coronary heart disease.

De Lorgeril M, Salen P.

In the recent years, the health effects of fish (and n-3 fatty acids) have attracted considerable scientific interest. The present consensus is that the cardioprotection of very long chain n-3 fatty acids (also called EPA and DHA) at the low dosage used in recent secondary prevention trials primarily results from an effect on the ischemic myocardium and probably not from an effect on blood lipids and hemostasis. In other words, at these low dosages, there is apparently no major effect of these fatty acids on the progression of the vascular atherosclerotic lesions. In contrast, dietary alpha-linolenic acid (ALA), the parent compound of the very long chain n-3 fatty acids occurring in some vegetable oils, may be protective through mechanisms other than the myocardial (anti-arrhythmic) ones. In addition to its own direct preventive effect on cardiac arrhythmias, dietary ALA actually inhibits the elongation and desaturation of linoleic acid (18:2 n-6) into arachidonic acid. Because arachidonic acid (20:4 n-6) plays an important role in inflammation (as the precursor of the proinflammatory eicosanoids and leukotrienes), modifying its amount in blood and cell membranes influences the prevalence and severity of eicosanoid-related disorders, including atherosclerotic complications. The present knowledge of n-3 fatty acids justifies that physicians, in particular cardiologists in the context of secondary prevention of coronary heart disease, manage their patients, the young and the old, to increase their consumption of these fatty acids. They can only advise them to adequately adapt their diet (for instance in primary prevention), but in most cases, the systematic prescription of capsules containing oils enriched in ALA and EPA + DHA will be, ethically and scientifically, an obligation.

Am J Cardiol. 2004 May 1;93(9):1119-23.

Meta-analysis of observational studies on fish intake and coronary heart disease.

Whelton SP, He J, Whelton PK, Muntner P.

Fish consumption has been associated with a lower risk of coronary heart disease (CHD) in some but not all studies. We conducted a meta-analysis of observational studies to determine if fish consumption is associated with lower fatal and total CHD. English language articles published before May 2003 were searched. In all, 19 observational studies (14 cohort and 5 case-control) in which there was a group that consumed fish on a regular basis and a comparison group that consumed little or no fish were included. With use of a standardized protocol and data extraction form, information on study design, sample size, participant characteristics, duration of follow-up, assessment of end points, and consumption of fish was abstracted. Using a random effects model, we pooled data from each study. Fish consumption versus little to no fish consumption was associated with a relative risk of 0.83 (95% confidence interval 0.76 to 0.90; $p < 0.005$) for fatal CHD and a relative risk of 0.86 (95% confidence interval 0.81 to 0.92; $p < 0.005$) for total CHD. The results indicate that fish consumption is associated with a significantly lower risk of fatal and total CHD. These findings suggest that fish consumption may be an important component of lifestyle modification for the prevention of CHD.

Curr Opin Clin Nutr Metab Care. 2004 Mar;7(2):131-6.

Omega-3 fatty acids and cardiovascular disease.

von Schacky C.

PURPOSE OF REVIEW: Omega-3 fatty acids are gaining acceptance in the cardiovascular field. The present review describes the most recent studies and developments in the field. RECENT FINDINGS: Marine omega-3 fatty acids, that is eicosapentaenoic and docosahexaenoic acids, prevent fatal myocardial infarction and sudden cardiac death by their antiarrhythmic effects and presumably also by their effect on infarct size, the latter mediated by plaque stabilization, improvements in endothelial function and other mechanisms. In contrast, a cardioprotective effect of alpha-linolenic acid, a plant-derived omega-3 fatty acid, remains to be clearly demonstrated in adequate intervention trials. Other forms of applications, like parenteral use or other indications, like in the psychiatric field, are currently being actively investigated. SUMMARY: Eicosapentaenoic and docosahexaenoic acids, but not alpha-linolenic acid, prevent sudden death and other cardiovascular catastrophies, and have therefore been recently incorporated into the pertinent guidelines of European and American cardiologic societies.

Prev Cardiol. 2003 Winter;6(1):38-41.

Consumption of fish and fish oils and decreased risk of stroke.

Skerrett PJ, Hennekens CH.

Consumption of fish and fish oils was first associated with decreased risk of cardiovascular disease almost 50 years ago. Since then, a number of epidemiologic studies have evaluated whether their consumption is specifically associated with stroke. Ecologic/cross-sectional and case-control studies have generally shown an inverse association between consumption of fish

and fish oils and stroke risk. Results from five prospective studies have been less consistent, with one showing no association, one showing a possible inverse association, and three demonstrating a significant inverse association. In the latest and largest of these, the Nurses Health Study, the relative risk of total stroke was lower, although not significantly so, among women who regularly ate fish than among those who did not. A significant decrease in the risk of thrombotic stroke (relative risk, 0.49; 95% confidence interval, 0.26-0.93) was observed among women who ate fish at least two times per week compared with women who ate fish less than once per month, after adjustment for age, smoking, and other cardiovascular risk factors; a nonsignificant decrease was observed among women in the highest quintile of long-chain omega-3 polyunsaturated fatty acid intake. No association was observed between consumption of fish or fish oil and hemorrhagic stroke. These data support the hypothesis that consumption of fish several times per week reduces the risk of thrombotic stroke but does not increase the risk of hemorrhagic stroke. Copyright 2003 CHF, Inc.

Am J Clin Nutr. 2003 Jul;78(1):65-71.

n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease.

Erkkila AT, Lehto S, Pyorala K, Uusitupa MI.

BACKGROUND: Data on the association of n-3 fatty acid content in serum lipids with mortality in patients with coronary artery disease (CAD) are limited. OBJECTIVE: We hypothesized that a high proportion of n-3 fatty acids in serum lipids would be associated with reduced risks of death and coronary events in patients with established CAD. DESIGN: We measured dietary intakes via food records and the fatty acid composition of serum cholesteryl esters (CEs) in 285 men and 130 women with CAD (x age: 61 y; range: 33-74 y). The patients participating in the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) study were followed up for 5 y. RESULTS: During the follow-up, 36 patients died, 21 had myocardial infarctions, and 12 had strokes. The relative risks (RRs) of death adjusted for cardiovascular disease risk factors for subjects in the highest tertile of fatty acids in CEs compared with those in the lowest tertile were 0.33 (95% CI: 0.11, 0.96) for alpha-linolenic acid, 0.33 (0.12, 0.93) for eicosapentaenoic acid, and 0.31 (0.11, 0.87) for docosahexaenoic acid (P for trend = 0.063, 0.056, and 0.026, respectively). A high proportion of eicosapentaenoic acid in CEs was associated with a low risk of CAD death. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death [1-57 g/d, RR = 0.50 (0.20, 1.28); > 57 g/d, RR = 0.37 (0.14, 1.00); P for trend = 0.059]. CONCLUSION: High proportions of n-3 fatty acids in serum lipids are associated with a substantially reduced risk of death.

QJM. 2003 Jul;96(7):465-80.

The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease.

Lee KW, Lip GY.

It has long been recognized from epidemiological studies that Greenland Eskimos have substantially reduced rates of acute myocardial infarction (MI) compared with Western controls. From these epidemiological observations, the benefits of fatty fish consumption have been explored in cell culture and animal studies, as well as randomized controlled trials investigating the cardioprotective effects of omega-3 fatty acids. Dietary omega-3 fatty acids seem to stabilize the myocardium electrically, resulting in reduced susceptibility to ventricular arrhythmias, thereby reducing the risk of sudden death. These fatty acids also have potent anti-inflammatory effects, and may also be antithrombotic and anti-atherogenic. Furthermore, the recent GISSI-Prevention study of 11 324 patients showed a marked decrease in risk of sudden cardiac death as well as a reduction in all-cause mortality in the group taking a highly purified form of omega-3 fatty acids, despite the use of other secondary prevention drugs, including beta-blockers and lipid-lowering therapy. The use of omega-3 fatty acids should be considered as part of a comprehensive secondary prevention strategy post-myocardial infarction.

Panminerva Med. 2003 Jun;45(2):99-107.

Omega-3 polyunsatured fatty acids role in postmyocardial infarction therapy.

Imazio M, Forno D, Quaglia C, Trinchero R.

Largely initiated by studies among Eskimos in the early 1970s, great attention has been given to possible effects of omega-3 polyunsatured fatty acids (PUFA) in cardiovascular diseases. A series of positive effects on pathogenetic mechanisms of cardiovascular disease has been discovered from laboratory studies in cell cultures, animal models and in humans. omega-3 PUFA can reduce platelets and leucocytes activities as well as plasma triglycerides. Moreover they can have antiarrhythmic properties. Nowadays patients who experienced myocardial infarction have decreased risk of total and cardiovascular mortality by treatment with omega-3 PUFA (1 g daily). This effect is present irrespective of high or low fish intake or simultaneous intake of other drugs for secondary prevention of coronary heart disease. Mainly on the basis of GISSI Prevention trial results, dietary supplementation with omega-3 PUFA is now recommended as a new component of secondary prevention after myocardial infarction in national and international guidelines.

Prev Cardiol. 2003 Summer;6(3):136-46.

Beyond the Mediterranean diet: the role of omega-3 Fatty acids in the prevention of coronary heart disease.

Harper CR, Jacobson TA.

Evidence from epidemiologic and clinical secondary prevention trials suggest that the omega-3 polyunsaturated fatty acids (n-3 PUFAs) may have a significant role in the prevention of coronary heart disease. Dietary sources of n-3 PUFAs include fish oils, rich in eicosapentaenoic acid and docosahexaenoic acid, along with plants rich in a-linolenic acid. Randomized secondary prevention clinical trials with fish oils (eicosapentaenoic acid, docosahexaenoic acid) and a-linolenic acid have demonstrated reductions in risk that compare favorably to those seen in landmark secondary prevention trials with lipid-lowering drugs. Several mechanisms explaining the cardioprotective effect of the n-3 PUFA have been suggested including antiarrhythmic and antithrombotic roles. Although official US guidelines for the dietary intake of n-3 PUFA are not available, several international guidelines have been published. Fish is an important source of the n-3 PUFA in the US diet; however, vegetable sources including grains and oils offer an alternative source for those who are unable to regularly consume fish.

Circulation. 2003 Apr 15;107(14):1852-7. Epub 2003 Mar 31.

Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women.

Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE.

BACKGROUND: Although several prospective cohort studies have found an inverse association between fish consumption and risk of coronary heart disease (CHD) or sudden cardiac death in the general population, limited data are available among diabetic patients. METHODS AND RESULTS: We examined prospectively the association between intake of fish and omega-3 fatty acids and risk of CHD and total mortality among 5103 female nurses with diagnosed type 2 diabetes but free of cardiovascular disease or cancer at baseline. Between 1980 and 1996 (45 845 person-years of follow-up), we documented 362 incident cases of CHD (141 CHD deaths and 221 nonfatal myocardial infarctions) and 468 deaths from all causes. Compared with women who seldom consumed fish (<1 serving/mo), the relative risks (RRs) (95% CI) of CHD adjusted for age, smoking, and other established coronary risk factors were 0.70 (0.48 to 1.03) for fish consumption 1 to 3 times per month, 0.60 (0.42 to 0.85) for once per week, 0.64 (0.42 to 0.99) for 2 to 4 times per week, and 0.36 (0.20 to 0.66) for 5 or more times per week (P for trend=0.002). Higher consumption of fish was also associated with a significantly lower total mortality (multivariate RR=0.48 [0.29 to 0.80] for > or =5 times per week [P for trend=0.005]). Higher consumption of long-chain omega-3 fatty acids was associated with a trend toward lower incidence of CHD (RR=0.69 [95% CI 0.47 to 1.03], P for trend=0.10) and total mortality (RR=0.63 [95% CI, 0.45 to 0.88], P for trend=0.02). CONCLUSIONS: A higher consumption of fish and long-chain omega-3 fatty acids was associated with a lower CHD incidence and total mortality among diabetic women.

Eur J Clin Nutr. 2003 Feb;57(2):193-200.

Lack of benefit of dietary advice to men with angina: results of a controlled trial.

Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NA, Elwood PC.

OBJECTIVE: To see whether mortality among men with angina can be reduced by dietary advice. DESIGN: A randomized controlled factorial trial. SETTING: Male patients of general practitioners in south Wales. SUBJECTS: A total of 3114 men under 70 y of age with angina. INTERVENTIONS: Subjects were randomly allocated to four groups: (1) advised to eat two portions of oily fish each week, or to take three fish oil capsules daily; (2) advised to eat more fruit, vegetables and oats; (3) given both the above types of advice; and (4) given no specific dietary advice. Mortality was ascertained after 3-9 y. RESULTS: Compliance was better with the fish advice than with the fruit advice. All-cause mortality was not reduced by either form of advice, and no other effects were attributable to fruit advice. Risk of cardiac death was higher among subjects advised to take oily fish than among those not so advised; the adjusted hazard ratio was 1.26 (95% confidence interval 1.00, 1.58; P=0.047), and even greater for sudden cardiac death (1.54; 95% CI 1.06, 2.23; P=0.025). The excess risk was largely located among the subgroup given fish oil capsules. There was no evidence that it was due to interactions with medication. CONCLUSIONS: Advice to eat more fruit was poorly complied with and had no detectable effect on mortality. Men advised to eat oily fish, and particularly those supplied with fish oil capsules, had a higher risk of cardiac death. This result is unexplained; it may arise from risk compensation or some other effect on patients' or doctors' behaviour.

Am J Clin Nutr. 2003 Feb;77(2):319-25.

n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study.

Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS.

BACKGROUND: Little is known about the relation of the dietary intake of n-3 polyunsaturated fatty acids, ie, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fatty fish and alpha-linolenic acid from vegetable oils, with ischemic heart disease among older adults. OBJECTIVE: We investigated the associations of plasma phospholipid concentrations of DHA, EPA, and alpha-linolenic acid as biomarkers of intake with the risk of incident fatal ischemic heart disease and incident nonfatal myocardial infarction in older adults. DESIGN: We conducted a case-control study nested in the Cardiovascular Health Study, a cohort study of adults aged > or = 65 y. Cases experienced incident fatal myocardial infarction and other ischemic heart disease death (n = 54) and incident nonfatal myocardial infarction (n = 125). Matched controls were randomly selected (n = 179). We measured plasma phospholipid concentrations of n-3 polyunsaturated fatty acids in blood samples drawn approximately 2 y before the event. RESULTS: A higher concentration of combined DHA and EPA was associated with a lower risk of fatal ischemic heart disease, and a higher concentration of alpha-linolenic acid with a tendency to lower risk, after adjustment for risk factors [odds ratio: 0.32 (95% CI: 0.13, 0.78; P = 0.01) and 0.52 (0.24, 1.15; P = 0.1), respectively]. In contrast, n-3 polyunsaturated fatty acids were not associated with nonfatal myocardial infarction. CONCLUSIONS: Higher combined dietary intake of DHA and EPA, and possibly alpha-linolenic acid, may lower the risk of fatal ischemic heart disease in older adults. The association of n-3 polyunsaturated fatty acids with fatal ischemic heart disease, but not with nonfatal myocardial infarction, is consistent with possible antiarrhythmic effects of these fatty acids.

Ann Pharmacother. 2002 Dec;36(12):1950-6.

Evidence for the cardioprotective effects of omega-3 Fatty acids.

Carroll DN, Roth MT.

OBJECTIVE: To review available literature regarding the cardiovascular effects of marine-derived Omega-3 fatty acids and evaluate the benefit of these fatty acids in the prevention of coronary heart disease. DATA SOURCES: Biomedical literature accessed through a MEDLINE search (1966-April 2002). Search terms included fish oil, omega-3 fatty acid, sudden death, hypertriglyceridemia, myocardial infarction, and mortality. DATA SYNTHESIS: Following an early 1970's observational investigation that Omega-3 fatty acids may reduce the occurrence of myocardial infarction-related deaths in Greenland Eskimos, additional trials have been conducted that support this finding. Epidemiologic and clinical trial data suggest that Omega-3 fatty acids may reduce the risk of cardiovascular-related death by 29-52%. In addition, the risk of sudden cardiac death was found to be reduced by 45-81%. Possible mechanisms for these beneficial effects include antiarrhythmic properties, improved endothelial function, antiinflammatory action, and reductions in serum triglyceride concentrations. Omega-3 Fatty acids are fairly well tolerated; potential adverse effects include bloating and gastrointestinal distress, "fishy taste" in the mouth, hyperglycemia, increased risk of bleeding, and a slight increase in low-density-lipoprotein cholesterol. CONCLUSIONS: Omega-3 Fatty acids may be beneficial and should be considered in patients with documented coronary heart disease. They may be particularly beneficial for patients with risk factors for sudden cardiac death.

JAMA. 2002 Apr 10;287(14):1815-21.

Fish and omega-3 fatty acid intake and risk of coronary heart disease in women.

Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE.

CONTEXT: Higher consumption of fish and omega-3 fatty acids has been associated with a lower risk of coronary heart disease (CHD) in men, but limited data are available regarding women. OBJECTIVE: To examine the association between fish and long-chain omega-3 fatty acid consumption and risk of CHD in women. DESIGN, SETTING, AND PARTICIPANTS: Dietary consumption and follow-up data from 84 688 female nurses enrolled in the Nurses' Health Study, aged 34 to 59 years and free from cardiovascular disease and cancer at baseline in 1980, were compared from validated questionnaires completed in 1980, 1984, 1986, 1990, and 1994. MAIN OUTCOME MEASURES: Incident nonfatal myocardial infarction and CHD deaths. RESULTS: During 16 years of follow-up, there were 1513 incident cases of CHD (484 CHD deaths and 1029 nonfatal myocardial infarctions). Compared with women who rarely ate fish (<1 per month), those with a higher intake of fish had a lower risk of CHD. After adjustment for age, smoking, and other cardiovascular risk factors, the multivariable relative risks (RRs) of CHD were 0.79 (95% confidence interval [CI], 0.64-0.97) for fish consumption 1 to 3 times per month, 0.71 (95% CI, 0.58-0.87) for once per week, 0.69 (95% CI, 0.55-0.88) for 2 to 4 times per week, and 0.66 (95% CI, 0.50-0.89) for 5 or more times per week (P for trend =.001). Similarly, women with a higher intake of omega-3 fatty acids had a lower risk of CHD, with multivariable RRs of 1.0, 0.93, 0.78, 0.68, and 0.67 (P<.001 for trend) across quintiles of intake. For fish intake and omega-3 fatty acids, the inverse association appeared to be stronger for CHD deaths (multivariate RR for fish consumption 5 times per week, 0.55 [95% CI, 0.33-0.90] for CHD deaths vs 0.73 [0.51-1.04]) than for nonfatal myocardial infarction. CONCLUSION: Among women, higher consumption of fish and omega-3 fatty acids is associated with a lower risk of CHD, particularly CHD deaths.

Cell Mol Life Sci. 2002 Mar;59(3):463-77.

Dietary n-3 polyunsaturated fatty acids and coronary heart disease-related mortality: a possible mechanism of action.

Demaison L, Moreau D.

Epidemiological and interventional studies indicate that dietary n-3 PUFA reduces mortality due to coronary heart disease (CHD). They act at a low dose, since one or two meals with fatty fish per week is sufficient to provide protection when compared with no fish intake. These fatty acids are effective in providing primary prevention in low- and high-risk subjects and secondary prevention. At high doses, dietary n-3 PUFAs have several beneficial properties. First, they act favourably on blood characteristics: they are hypocholesterolemic and hypotriglyceridemic; they reduce platelet aggregation; they exhibit antithrombotic and fibrinolytic activities; they reduce blood viscosity and they exhibit antiinflammatory action. Second, they reduce ischemia/reperfusion-induced cellular damage. This effect is apparently due to the incorporation of eicosapentaenoic acid in membrane phospholipids. Third, they reduce ischemia and reperfusion arrhythmias. All the effects exerted by n-3 PUFAs at high doses are incompatible with the beneficial action on CHD mortality in humans observed at low doses, where their main properties are related to circulation in the form of free fatty acids. Numerous experimental studies have indicated that low concentrations of exogenous n-3 PUFAs reduce the severity of cardiac arrhythmias. This effect is probably responsible for the protective action of n-3 PUFA on CHD mortality. Further studies are necessary to confirm this assumption in animals. Such studies should take account of the fact that only a low dose of n-3 PUFA (20 mg/kg/day) is necessary to afford protection. Furthermore, since the beneficial effect of n-3 PUFAs on CHD mortality is observed in fish eaters versus no-fish eaters, and since populations in industrialised countries consume excess n-6 PUFAs, control animals in long-term dietary experiments should be fed a diet with only n-6 fatty acids as a source of PUFAs.

Am J Med. 2002 Mar;112(4):298-304.

N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials.

Bucher HC, Hengstler P, Schindler C, Meier G.

PURPOSE: Observational studies have shown an inconsistent association between n-3 polyunsaturated fatty acids and the risk of coronary heart disease. We investigated the effects of dietary and non-dietary (supplemental) intake of n-3 polyunsaturated fatty acids on coronary heart disease. SUBJECTS AND METHODS: We searched the literature to identify randomized controlled trials that compared dietary or non-dietary intake of n-3 polyunsaturated fatty acids with a control diet or placebo in patients with coronary heart disease. Studies had to have at least 6 months of follow-up data, and to have reported clinical endpoint data. We identified 11 trials, published between 1966 and 1999, which included 7951 patients in the intervention and 7855 patients in the control groups. RESULTS: The risk ratio of nonfatal myocardial infarction in patients who were on n-3 polyunsaturated fatty acid-enriched diets compared with control diets or placebo was 0.8 (95% confidence interval [CI]: 0.5 to 1.2, P = 0.16; Breslow-Day test for heterogeneity, P = 0.01), and the risk ratio of fatal myocardial infarction was 0.7 (95% CI: 0.6 to 0.8, P <0.001; heterogeneity P >0.20). In 5 trials, sudden death was associated with a risk ratio of 0.7 (95% CI: 0.6 to 0.9, P <0.01; heterogeneity P >0.20), whereas the risk ratio of overall mortality was 0.8 (95% CI: 0.7 to 0.9, P <0.001; heterogeneity P >0.20). There was no difference in summary estimates between dietary and non-dietary interventions of n-3 polyunsaturated fatty acids for all endpoints. CONCLUSION: This meta-analysis suggests that dietary and non-dietary intake of n-3 polyunsaturated fatty acids reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with coronary heart disease.

Circulation. 2001 Nov 6;104(19):2269-72.

n-3 Polyunsaturated fatty acids, fish, and nonfatal acute myocardial infarction.

Tavani A, Pelucchi C, Negri E, Bertuzzi M, La Vecchia C.

BACKGROUND: The relation between n-3 polyunsaturated fatty acids (PUFAs), fish intake, and risk of coronary heart disease is controversial. METHODS AND RESULTS: An Italian case-control study including 507 patients with nonfatal acute myocardial infarction (AMI) and 478 hospital controls found a multivariate odds ratio (OR) of 0.67 (95% CI, 0.47 to 0.95) for the highest n-3 PUFA intake and 0.68 (95% CI, 0.47 to 0.98) for an intake of >1 portion of fish per week compared with >/=2 portions per week. CONCLUSIONS: Small amounts of n-3 PUFAs may be inversely related to AMI risk in this low-risk population.

Am J Clin Nutr. 2001 Oct;74(4):464-73.

n-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik.

Dewailly E, Blanchet C, Lemieux S, Sauve L, Gingras S, Ayotte P, Holub BJ.

BACKGROUND: Inuit traditionally consume large amounts of marine foods rich in n-3 fatty acids. Evidence exists that n-3 fatty acids have beneficial effects on key risk factors for cardiovascular disease. OBJECTIVE: Our goal was to verify the relation between plasma phospholipid concentrations of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and various cardiovascular disease risk factors among the Inuit of Nunavik, Canada. DESIGN: The study population consisted of 426 Inuit aged 18-74 y who participated in a 1992 health survey. Data were obtained through home interviews and clinical visits. Plasma samples were analyzed for phospholipid fatty acid composition. RESULTS: Expressed as the percentage of total fatty acids, geometric mean concentrations of EPA, DHA, and their combination in plasma phospholipids were 1.99%, 4.52%, and 6.83%, respectively. n-3 Fatty acids were positively associated with HDL-cholesterol concentrations and inversely associated with triacylglycerol concentrations and the ratio of total to HDL cholesterol. In contrast, concentrations of total cholesterol, LDL cholesterol, and plasma glucose increased as n-3 fatty acid concentrations increased. There were no significant associations between n-3 fatty acids and diastolic and systolic blood pressure and plasma insulin. CONCLUSIONS: Consumption of marine products, the main source of EPA and DHA, appears to beneficially affect some cardiovascular disease risk factors. The traditional Inuit diet, which is rich in n-3 fatty acids, is probably responsible for the low mortality rate from ischemic heart disease in this population.

Am J Clin Nutr. 2001 Jul;74(1):50-6.

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.

Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L.

BACKGROUND: Results of epidemiologic studies and clinical trials indicate that moderate doses of n-3 fatty acids reduce the risk of cardiovascular disease and may improve prognosis. OBJECTIVE: The objective was to evaluate the effect of a high-dose ethylester concentrate of n-3 fatty acids administered early after an acute myocardial infarction (MI) on subsequent cardiac events and serum lipids. DESIGN: Three hundred patients with acute MI were randomly assigned to a daily dose of either 4 g highly concentrated n-3 fatty acids or corn oil, administered in a double-blind manner over 12-24 mo. Median follow-up time was 1.5 y. Clinical follow-up, including the drawing of blood samples, was performed after 6 wk of treatment and later at 0.5-year intervals. RESULTS: Forty-two (28%) patients in the n-3 group and 36 (24%) in the corn oil group experienced at least one cardiac event (cardiac death, resuscitation, recurrent MI, or unstable angina). No significant difference in prognosis was observed between groups for single or combined cardiac events. Total cholesterol concentrations decreased in both groups, with no significant intergroup differences. On average, the monthly increase in HDL cholesterol was 1.11% in the n-3 group and 0.55% in the corn oil group ($P = 0.0016$). Triacylglycerol concentrations decreased by 1.30%/mo in the n-3 group, whereas they increased by 0.35%/mo in the corn oil group ($P < 0.0001$). CONCLUSION: No clinical benefit of a high-dose concentrate of n-3 fatty acids compared with corn oil was found despite a favorable effect on serum lipids.

Lipids. 2001;36 Suppl:S119-26.

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.

Marchioli R, Schweiger C, Tavazzi L, Valagussa F.

Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)-Prevenzione was conceived as a population, pragmatic trial on patients with recent myocardial infarctions conducted in the framework of the Italian public health system. In GISSI-Prevenzione, patients were invited to follow Mediterranean dietary habits, and were treated with up-to-date preventive pharmacological interventions. Long-term n-3 PUFA (1 g daily) but not vitamin E (300 mg daily) was beneficial for death and for combined death, nonfatal myocardial infarction, and stroke. All the benefit, however, was attributable to the decrease in risk for overall, cardiovascular, cardiac, coronary, and sudden death. At variance with the orientation of a scientific scenario largely dominated by the "cholesterol-heart hypothesis," GISSI-Prevenzione results indicate n-3 PUFA (virtually devoid of any cholesterol-lowering effect) as a relevant pharmacological treatment for secondary prevention after myocardial infarction. As to the relevance and comparability of GISSI-Prevenzione results, up to 5.7 lives could be saved every 1000 patients with previous myocardial infarction treated with n-3 PUFA (1 g daily) per year. Such a result is comparable to that observed in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, where 5.2 lives could be saved per 1000 hypercholesterolemic, coronary heart disease patients treated with pravastatin for 1 yr. The choice of a relatively low-dose regimen (1-g capsule daily) more acceptable for long-term treatment in a population of patients following Mediterranean dietary habits, and the pattern of effects seen in GISSI-Prevenzione (namely, reduction of overall mortality with no decrease in the rate of nonfatal myocardial infarction) all strongly suggest that n-3 PUFA treatment should be considered a recommended new component of secondary prevention. The importance of this combined/additive effect is further suggested by the analyses of the interplay

between diet and n-3 PUFA: There is an interesting direct correlation between size of the effect and "correctness" of background diets. It can be anticipated that a conceptual barrier must be overcome: A "dietary drug" should be added to "dietary advice," which remains fundamental to allow this statement to become true in clinical practice.

Lipids. 2001;36 Suppl:S99-102.

The effect of n-3 fatty acids on coronary atherosclerosis: results from SCIMO, an angiographic study, background and implications.

von Schacky C, Baumann K, Angerer P.

According to the model of "response to injury," the arterial endothelium is occasionally injured in hyperlipidemia, hypertension, diabetes mellitus and in other states known as risk factors. The ensuing inflammatory response is modulated by cytokines and growth factors, among them platelet-derived growth factor (PDGF), and monocyte chemoattractant protein-1 (MCP-1). In two independent studies, we demonstrated that mRNA levels for PDGF-A and -B and for MCP-1 are reduced after ingestion of n-3 fatty acids by human volunteers. This reduction persists after monocyte stimulation/differentiation by adherence. Moreover, the reduction is brought about only by dietary n-3 fatty acids and not by other classes of unsaturated fatty acids (n-6 or n-9). This appears to be one major mechanism of action of reduced progression/increased regression of established coronary artery disease by ingestion of 1.5 g/d n-3 fatty acids, as assessed by coronary angiography in a randomized placebo-controlled double-blind intervention study in 223 patients. The study was conducted according to "Good Clinical Practice," comprehensive rules regulating investigations with pharmaceutical compounds. Together, our investigations lend support to the importance of PDGF-A, PDGF-B, and MCP-1 in the pathogenesis of atherosclerosis, and the beneficial role of n-3 fatty acids therein.

Lipids. 2001;36 Suppl:S79-82.

n-3 polyunsaturated fatty acids and coronary thrombosis.

Kristensen SD, Iversen AM, Schmidt EB.

Studies of Greenland Eskimos showed that a very high intake of marine n-3 fatty acids markedly inhibited platelet reactivity and suggested that intake of these fatty acids might prevent coronary thrombosis. Later studies with lower, more practical doses of n-3 fatty acids also have shown a platelet inhibitory effect of n-3 fatty acids, albeit fairly marginal. Furthermore, n-3 fatty acids have little effect on measures of blood coagulability and may slightly decrease fibrinolysis. In animal models, n-3 fatty acids often have been shown to inhibit thrombosis, but again the doses have tended to be very high. Finally, there has been little effect of (low-dose) n-3 fatty acids in clinical trials in humans on the incidence of myocardial infarction. Overall, there is little evidence for a major antithrombotic effect of practical doses of n-3 fatty acids on coronary thrombosis. This does not exclude a beneficial effect of n-3 fatty acids on coronary heart disease as suggested from clinical trials, but the major effect may be antiarrhythmic rather than antithrombotic.

Circulation. 2000 Nov 28;102(22):2677-9.

Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study.

Rissanen T, Voutilainen S, Nyyssonen K, Lakka TA, Salonen JT.

BACKGROUND: Previous findings concerning the serum levels of fish-derived (n-3) fatty acids and coronary heart disease are inconsistent. The purpose of this study was to investigate the association between the serum n-3 end-product fatty acids docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid and the risk of acute coronary events in middle-aged men. METHODS AND RESULTS: We studied this association in the Kuopio Ischaemic Heart Disease Risk Factor Study, a prospective population study in Eastern Finland. Subjects were randomly selected and included 1871 men aged 42 to 60 years who had no clinical coronary heart disease at baseline examination. A total of 194 men had a fatal or nonfatal acute coronary event during follow-up. In a Cox proportional hazards' model adjusting for other risk factors, men in the highest fifth of the proportion of serum DHA+DPA in all fatty acids had a 44% reduced risk (P=0.014) of acute coronary events compared with men in the lowest fifth. Men in the highest fifth of DHA+DPA who had a low hair content of mercury (</=2.0 microgram/g) had a 67% reduced risk (P=0.016) of acute coronary events compared with men in the lowest fifth who had a high hair content of mercury (>2.0 microgram/g). There was no association between proportion of eicosapentaenoic acid and the risk of acute coronary events. CONCLUSIONS: Our data provide further confirmation for the concept that fish oil-derived fatty acids reduce the risk of acute coronary events. However, a high mercury content in fish could attenuate this protective effect.

Am J Clin Nutr. 2000 Jan;71(1 Suppl):224S-7S.

n-3 fatty acids and the prevention of coronary atherosclerosis.

von Schacky C.

Epidemiologic studies have shown an inverse correlation between consumption of fish or other sources of dietary n-3 fatty acids and cardiovascular events. Numerous mechanisms of action for the favorable effect of dietary n-3 fatty acids on factors implicated in the pathogenesis of atherosclerosis have been described. Studies in dogs, swine, and nonhuman primates have consistently shown beneficial effects in various models of vasoocclusive diseases. Studies published currently do not indicate that dietary n-3 fatty acids prevent restenosis after percutaneous coronary angioplasty or induce regression of coronary atherosclerosis. However, in a recent study, occlusion of aortocoronary venous bypass grafts was reduced after 1 y by daily ingestion of 4 g fish-oil concentrate. In the Diet and Reinfarction Trial, 2-y overall mortality was reduced by 29% in survivors of a first myocardial infarction after consumption of n-3 fatty acid-rich fatty fish at least twice a week had been advised (Lancet 1989;2:757-61). When n-3 fatty acids were integrated into a diet resembling a traditional Mediterranean diet, 5-y cardiovascular mortality after a first myocardial infarction was reduced by 70% (Lancet 1994; 343:1454-9). Preliminary studies indicate that cardiac transplant patients could be an interesting focus of investigation. Currently, food sources rich in n-3 fatty acids are thought to be beneficial in secondary prophylaxis after a myocardial infarction. Large-scale clinical studies with endpoints such as morbidity and mortality are needed to more precisely define the role of n-3 fatty acids in primary and secondary prophylaxis of coronary atherosclerosis.

Eur J Clin Nutr. 1999 Aug;53(8):585-90.

Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies.

Marckmann P, Gronbaek M.

OBJECTIVES: To review all prospective cohort studies examining the relationship between fish intake and coronary heart disease mortality, and to assess the strength and consistency of their findings. DESIGN: Systematic review of studies based on individual records of fish or n-3 polyunsaturated fatty acid consumption and coronary heart disease death. Studies were given scientific quality scores and divided into categories of high, intermediate, or insufficient quality. MAIN OUTCOME MEASURE: Coronary heart disease mortality. RESULTS: Eleven studies were identified. The cohorts counted a total of 116764 individuals. Of four studies judged to be of high quality, the two largest (n = 44895 and 20051) were performed in populations at low risk of coronary heart disease. They found no protective effect of fish consumption. The other two high-quality studies were relatively small (n = 852 and 1822) and included individuals at higher risk. They both found an inverse relationship between fish consumption and coronary heart disease death, suggesting that 40-60 g fish per day is optimal and associated with a risk reduction of 40-60%. Results of four studies of intermediate quality support that fish consumption is inversely associated with coronary heart disease mortality in high-risk populations only. Three studies were judged to be of insufficient quality to be used for drawing conclusions. CONCLUSIONS: Fish consumption is not associated with reduced coronary heart disease mortality in low-risk populations. However, fish consumption at 40-60 g daily is associated with markedly reduced coronary heart disease mortality in high-risk populations. The underlying biochemical mechanism is not known and causal inference premature.

Arterioscler Thromb Vasc Biol. 1999 Jul;19(7):1681-6.

The effect of supplementation with omega-3 fatty acids on soluble markers of endothelial function in patients with coronary heart disease.

Johansen O, Seljeflot I, Hostmark AT, Arnesen H.

During progression of atherosclerosis the overlying endothelial cells alter their expression of some surface molecules. Circulating levels of such molecules may be quantified. We investigated the effect of omega-3 fatty acids (n-3 FA) on the levels of tissue plasminogen activator antigen, von Willebrand factor, and the soluble forms of thrombomodulin, P-selectin, E-selectin, and vascular cell adhesion molecule-1 in 54 patients with coronary heart disease. Twenty-three of the patients had taken 5.1 g/d n-3 FA for 6 months (group I) and 31 were given corn oil as placebo (group II). For another 4 weeks ("the study period") they all got 5.1 g/d of n-3 FA. Compliance was confirmed by demonstration of changes in relevant fatty acids in serum phospholipids. At baseline, significant differences between the groups were found with lower median values of von Willebrand factor (128% versus 147%) and soluble thrombomodulin (24.9 versus 32.5 ng/mL) and higher median values of soluble E-selectin (41.4 versus 35.5 ng/mL) and soluble vascular cell adhesion molecule-1 (573 versus 473 ng/mL) in group I. During the study period differences in changes between the groups were found; tissue plasminogen activator antigen and soluble thrombomodulin decreased (P for difference between the groups 0.001 and 0.015, respectively), whereas soluble E-selectin and soluble vascular cell adhesion molecule-1 increased (P for difference between the groups <0.01 for both) in group II relative to group I. Our results indicate that n-3 FA supplementation decreases hemostatic markers of atherosclerosis, whereas markers of inflammation may be increased. The latter may be the result of lipid peroxidation as a simultaneous decrease of vitamin E and increase in thiobarbituric acid-reactive substances were observed.

Ann Intern Med. 1999 Apr 6;130(7):554-62.

The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial.

von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H.

BACKGROUND: Epidemiologic studies, studies of mechanisms of action, and many animal studies indicate that dietary intake of omega-3 fatty acids has antiatherosclerotic potential. Few trials in humans have examined this potential. OBJECTIVE: To determine the effect of dietary intake of omega-3 fatty acids on the course of coronary artery atherosclerosis in humans. DESIGN: Randomized, double-blind, placebo-controlled, clinically controlled trial. SETTING: University preventive cardiology unit. PATIENTS: 223 patients with angiographically proven coronary artery disease. INTERVENTION: Fish oil concentrate (55% eicosapentaenoic and docosahexaenoic acids) or a placebo with a fatty acid composition resembling that of the average European diet, 6 g/d for 3 months and then 3 g/d for 21 months. MEASUREMENTS: The results of standardized coronary angiography, done before and after 2 years of treatment, were evaluated by an expert panel (primary end point) and by quantitative coronary angiography. Patients were followed for clinical and laboratory status. RESULTS: Pairs of angiograms (one taken at baseline and one taken at 2 years) were evaluated for 80 of 112 placebo recipients and 82 of 111 fish oil recipients. At the end of treatment, 48 coronary segments in the placebo group showed changes (36 showed mild progression, 5 showed moderate progression, and 7 showed mild regression) and 55 coronary segments in the fish oil group showed changes (35 showed mild progression, 4 showed moderate progression, 14 showed mild regression, and 2 showed moderate regression) ($P = 0.041$). Loss in minimal luminal diameter, as assessed by quantitative coronary angiography, was somewhat less in the fish oil group ($P > 0.1$). Fish oil recipients had fewer cardiovascular events ($P = 0.10$); other clinical variables did not differ between the study groups. Low-density lipoprotein cholesterol levels tended to be greater in the fish oil group. CONCLUSION: Dietary intake of omega-3 fatty acids modestly mitigates the course of coronary atherosclerosis in humans.

Am J Clin Nutr. 1997 Oct;66(4 Suppl):1020S-1031S.

Are fish oils beneficial in the prevention and treatment of coronary artery disease?

Connor SL, Connor WE.

The n-3 fatty acids of fish and fish oil have great potential for the prevention and treatment of patients with coronary artery disease. Unlike many of the pharmaceutical agents used in patients with coronary artery disease that have just a single mechanism of action, the eicosapentaenoic and docosahexaenoic acids of fish oil have multifaceted actions. One of their most important effects is the prevention of arrhythmias, with documentation derived from experiments in cultured myocytes, experiments in animals, epidemiologic correlations, and clinical trials. Especially important is the ability of these n-3 fatty acids to inhibit ventricular fibrillation and consequent cardiac arrest. Eicosapentaenoic acid has several antithrombotic actions, particularly in inhibiting the synthesis of thromboxane A2, the prostaglandin that causes platelet aggregation and vasoconstriction. Fish oil retards the growth of the atherosclerotic plaque by inhibiting both cellular growth factors and the migration of monocytes. The n-3 fatty acids promote the synthesis of the beneficial nitric oxide in the endothelium. Experiments in humans indicate a profound hypolipidemic effect of fish oil, especially lowering of plasma triacylglycerol. Both very-low-density lipoprotein

production and apolipoprotein B synthesis are inhibited by fish oil. Finally, fish oil has a mild blood pressure-lowering effect in both normal and mildly hypertensive individuals. These composite effects suggest a prominent therapeutic role for fish oil in the prevention and treatment of coronary artery disease.

Int J Cardiol. 1998 Sep 1;66(1):31-8.

Effect of serum fatty acid composition on coronary atherosclerosis in Japan.

Hojo N, Fukushima T, Isobe A, Gao T, Shiwaku K, Ishida K, Ohta N, Yamane Y.

The serum lipid profiles of patient's with or without significant coronary stenosis diagnosed by coronary angiography and of control subjects were compared. The level of high-density-lipoprotein cholesterol and eicosapentaenoic acid were significantly lower in the patients with significant coronary stenosis than in the control subjects. It suggests that high-density-lipoprotein cholesterol and omega3 fatty acids may have a protective effect on the progress of coronary atherosclerosis. The frequency of eating dark-meat fish was positively associated with serum eicosapentaenoic acid and docosahexaenoic acid, omega3 fatty acids, and inversely associated with serum stearic acid and linoleic acid. The frequency of eating soybean products was positively associated with serum docosahexaenoic acid and inversely associated with serum linoleic acid. It is necessary to discuss a way to popularise a diet of dark-meat fish and soybean products as a means of preventing coronary heart disease.

Cardiovasc Drugs Ther. 1997 Jul;11(3):485-91.

Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival--4.

Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.

In a randomized, placebo-controlled trial, the effects of treatment with fish oil (eicosapentaenoic acid, 1.08 g/day) and mustard oil (alpha-linolenic acid, 2.9 g/day) were compared for 1 year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with suspected acute myocardial infarction (AMI). Treatments were administered about (mean) 18 hours after the symptoms of AMI in all three groups. The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study. After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.

Am J Cardiol. 1995 Sep 1;76(7):459-62.

Comparison of effects of N-3 to N-6 fatty acids on serum level of lipoprotein(a) in patients with coronary artery disease.

Herrmann W, Biermann J, Kostner GM.

The influence of dietary supplementation with n-3 versus n-6 fatty acids on plasma lipoprotein(a) (Lp[a]) levels was studied. Thirty-five male hospitalized patients with coronary artery disease were treated for 4 weeks with 12 g/day of fish oil (approximately 8.5 g of n-3 fatty acids) in combination with a 5,000 kilojoule, 30% fat diet and moderate exercise. Eighteen control patients given the same dietary and training program were treated with 12 g/day of rapeseed oil. Plasma Lp(a), in addition to several lipids and lipoproteins, blood clotting factors, and platelet reactivity, were measured before and at the end of therapy. Results can be summarized as follows: total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B levels decreased significantly in both the rapeseed oil (-14.4%, -20.3%, -15.2%, respectively) and fish oil (-12.2%, -16.0%, and -14.2%, respectively) groups. Triglycerides decreased (-20.3%) and high-density lipoprotein cholesterol increased (+8.3%) significantly only in patients treated with fish oil. Plasma Lp(a) levels were reduced by 14% in the fish oil group, but unaffected in the rapeseed oil group. Patients treated with fish oil could be categorized into 2 subgroups: "responders," with a reduction in Lp(a) by 24% and "nonresponders," with a small nonsignificant increase in serum Lp(a). Responders and nonresponders exhibited a marked reduction in cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and an increase in high-density lipoprotein3 cholesterol. There was a large reduction in tissue plasminogen activator in the fish oil group, which correlated significantly with reduction in Lp(a).(ABSTRACT TRUNCATED AT 250 WORDS)

J Am Coll Cardiol. 1995 Jun;25(7):1492-8.

Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group.

Sacks FM, Stone PH, Gibson CM, Silverman DI, Rosner B, Pasternak RC.

OBJECTIVES. This randomized clinical trial tested whether fish oil supplements can improve human coronary atherosclerosis. BACKGROUND. Epidemiologic studies of populations whose intake of oily fish is high, as well as laboratory studies of the effects of the polyunsaturated fatty acids in fish oil, support the hypothesis that fish oil is antiatherogenic. METHODS. Patients with angiographically documented coronary heart disease and normal plasma lipid levels were randomized to receive either fish oil capsules (n = 31), containing 6 g of n-3 fatty acids, or olive oil capsules (n = 28) for an average duration of 28 months. Coronary atherosclerosis on angiography was quantified by computer-assisted image analysis. RESULTS. Mean (+/- SD) baseline characteristics were age 62 +/- 7 years, plasma total cholesterol concentration 187 +/- 31 mg/dl (4.83 +/- 0.80 mmol/liter) and triglyceride levels 132 +/- 70 mg/dl (1.51 +/- 0.80 mmol/liter). Fish oil lowered triglyceride levels by 30% ($p = 0.007$) but had no significant effects on other plasma lipoprotein levels. At the end of the trial, eicosapentaenoic acid in adipose tissue samples was 0.91% in the fish oil group compared with 0.20% in the control group ($p < 0.0001$). At baseline, the minimal lumen diameter of coronary artery lesions (n = 305) was 1.64 +/- 0.76 mm, and percent narrowing was 48 +/- 14%. Mean minimal diameter of atherosclerotic coronary arteries decreased by 0.104 and 0.138 mm in the fish oil and

control groups, respectively (p = 0.6 between groups), and percent stenosis increased by 2.4% and 2.6%, respectively (p = 0.8). Confidence intervals exclude improvement by fish oil treatment of > 0.17 mm, or > 2.6%. CONCLUSIONS. Fish oil treatment for 2 years does not promote major favorable changes in the diameter of atherosclerotic coronary arteries.

Curr Med Res Opin. 1990;12(1):1-11.

A placebo-controlled, double-blind study of eicosapentaenoic acid-rich fish oil in patients with stable angina pectoris.

Solomon SA, Cartwright I, Pockley G, Greaves M, Preston FE, Ramsay LE, Waller PC.

A study was carried out to evaluate the clinical and haematological effects of dietary supplementation with eicosapentaenoic acid (EPA)-rich fish oil (MaxEPA', 2.8 g EPA daily) compared to placebo (olive oil) in 10 patients with stable angina pectoris. After 3 months, there was a significant increase in red cell deformability (p less than 0.001), reduced whole blood viscosity (p less than 0.02), and prolonged skin bleeding time (p less than 0.001) in the fish oil group compared to the placebo group. Haematocrit, plasma viscosity, fibrinogen concentration, platelet count, and in vitro platelet aggregation were unaltered. No significant symptomatic or objective improvement was noted in angina pectoris in either group despite the significant rheological changes produced in the patients receiving fish oil.

Lancet. 1989 Sep 30;2(8666):757-61.

Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART).

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM.

A randomised controlled trial with a factorial design was done to examine the effects of dietary intervention in the secondary prevention of myocardial infarction (MI). 2033 men who had recovered from MI were allocated to receive or not to receive advice on each of three dietary factors: a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat, an increase in fatty fish intake, and an increase in cereal fibre intake. The advice on fat was not associated with any difference in mortality, perhaps because it produced only a small reduction (3-4%) in serum cholesterol. The subjects advised to eat fatty fish had a 29% reduction in 2 year all-cause mortality compared with those not so advised. This effect, which was significant, was not altered by adjusting for ten potential confounding factors. Subjects given fibre advice had a slightly higher mortality than other subjects (not significant). The 2 year incidence of reinfarction plus death from ischaemic heart disease was not significantly affected by any of the dietary regimens. A modest intake of fatty fish (two or three portions per week) may reduce mortality in men who have recovered from MI.

Acta Med Scand. 1976;200(1-2):69-73.

The composition of food consumed by Greenland Eskimos.

Bang HO, Dyerberg J, Hjoorne N.

Food specimens have been collected, by means of the double-portion technique, from Greenland Eskimo hunters and their wives, in all seven persons, on seven consecutive days. Their food was found to contain more protein and less carbohydrates than average Danish food and an almost equal amount of fat. Compared with Danish food, the fatty acid pattern of the consumed lipids--essentially of mammalian marine origin--showed a higher content of long chain polyunsaturated fatty acids (especially C20:5) and lower contents of linoleic and linolenic acids. However, the sum of the polyunsaturated fatty acids was smaller than in Danish food. Using Keys' formula, describing the serum cholesterol level as a function of the nutritional fatty acids, the essentially lower serum choelsterol level found in Greenland Eskimos was not explained by our findings. It is suggested instead to be a special metabolic effect of the long chain polyunsaturated fatty acids from marine mammals. There might be a similar effect on the plasma triglyceride and very low density lipoprotein concentrations, explaining the much lower plasma concentrations of these components in Eskimos than in Western populations. Our findings might have an essential bearing on the difference in morbidity from coronary atherosclerotic disease between these populations.

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