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CARDIOVASCULAR HEALTH EFFECTS OF FISH

WITH SPECIAL ATTENTION ON THE QUANTIFIABLE BENEFITS AMONG GENERAL POPULATION

For BENERIS

Benefit-risk assessment for food: an iterative value-of-information approach

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Introduction

Beneris (Benefit-risk assessment for food: an iterative value-of-information approach) - project aims to develop and test the functionality of the novel risk-benefit assessment model. Within Beneris-project this novel method is applied for the estimation of overall health effects and risks of fish consumption. For this purpose quantified data on the health benefits of fish is needed. This deliverable reviews the cardiovascular health benefits of fish and its constituents with emphasis on the applicability of diverse available data for general population and different age groups.

The cardiovascular health effects of fish and its constituents like omega-3 fatty acids and selenium have been studied in number of epidemiological and clinical studies. However, clinical diversity complicates the available data as the type of participants, interventions and measured outcomes vary greatly in these studies.

In most cases, data on cardiovascular effects of fish consumption has been gained from large cohort studies like Chigaco Western Electric Study (Daviglus et al. 1997) and Nurses Health Study (Hu et al. 2002) among general population, whereas effects of omega-3 fatty acids have been examined in clinical trials like GISSI-Prevenzione trial (Marchioli et al. 2002, GISSI-Prevenzione investigators 1999) among patients with cardiovascular disease. Moreover, the data is further convoluted by various end points of interest, as studies have followed different cardiovascular disease outcomes from events like myocardial infarction or stroke to death.

In addition to disease outcomes, the effects of fish on risk factors of cardiovascular disease have been examined. Since plausible mechanisms for the protective role of omega-3 fatty acids in fish have included antiarrhythmic, antithrombotic, antiatherosclerotic and anti-inflammatory effects, blood pressure and triglyceride lowering capability and potency to improve endothelial function (Din et al. 2004), a large number of heterogenous studies has also been conducted to assess these risk markers. Even there are no direct data linking childhood risk factors to adult cardiovascular disease, there is evidence that children and adolescents with several risk factors like dyslipidemia and elevated blood pressure are at increased risk of developing atherosclerosis in adulthood (Raitakari et al. 2003).

Several meta-analyses on the cardiovascular health benefits of fish, fish oils or omega-3 fatty acids have been published during the recent years. These meta-analyses have covered different areas of cardiovascular health including *total and cardiovascular mortality* (Wang et al. 2006, König et al. 2005, Hooper et al. 2004, Yzebe and Lievre 2004, He et al. 2004 a, Carroll and Roth 2002, Guallar Castillon et al. 1993), *stroke risk* (Bouzan et al. 2005, He et al. 2004 b, Morris et al. 1993), *coronary heart disease* (Whelton et al. 2004) and *various risk factors of cardiovascular disease* (Balk et al. 2006, Morris et al. 1993). Even studies on benefit-risk by dose curves have been published (Gochfeld and Burger 2005, Mozaffarian and Rimm 2006).

It is not always clear to which age groups the meta-analyses apply and furthermore, whether the results are applicable for general population (primary prevention studies), risk groups like hypercholesterolemic subjects or subjects with evident disease (secondary prevention studies). Therefore, there was a need to further organize this abundance of data in form that could be used in benefit-risk-assessment.

Objective

The aim of the work presented here was to collect quantified data on cardiovascular health benefits of fish in a feasible form to be used in the Fish-case study of Beneris (Benefit-risk assessment for food: an iterative value-of-information approach) -project.

Methods

The cardiovascular benefits were examined by reviewing the meta-analyses indexed in Medline on fish, selenium, omega-3 fatty acids, EPA and DHA. Furthermore the search was extended to some systematic reviews to expand the view on topic of interest. The work was based on altogether 37 articles, of which 19 were meta-analyses or systematic reviews on fish or omega-3 fatty acids (See appendix 1 and 2 for brief description) and one meta-analysis on selenium (Flores-Mateo et al. 2006). In addition 18 original studies (see appendix 3 for a list) were examined to verify the data and deepen the understanding on the applicability of the results of the meta-analyses for the European population.

Overview of results and discussion

The major cardiovascular outcomes and risk factors that have been of interest in studies on the cardiovascular health effects of fish are illustrated in figure 1. The figure also gives reference to studies with most applicable dose-response data. Dose-response data on cardiovascular disease outcomes is summarized in table 1 and on CVD risk factors in table 2. There is applicable dose-response data on cardiovascular disease outcomes for adult population, but insufficient data to extend this information for children. As to the studies on risk markers, they have also been conducted among adults, but the dose-responses presented for adult population should be applicable also for children and adolescents.

All-cause mortality, total cardiovascular mortality and combined cardiovascular events

Results of meta-analyses addressing total mortality and fish or omega-3 fatty acids have ranged from no effect (Hooper et al. 2004) to 16-17 % reduction in relative risk (Mozaffarian and Rimm 2006, Yzebe et al. 2004.) Mozaffarian and Rimm (2006) calculated a 17 % reduction in relative risk of all cause mortality with at least 1-2 servings of fish/ week. This calculation was considered as the most applicable as the two other meta-analyses did not provide clear dose-response information.

As to the cardiovascular-related death, Carroll et al. (2002) proposed that omega-3 fatty acids (1-2 servings of fish/ week or EPA/ DHA supplements 850 mg/day) may reduce the risk by 29-52%. Conversely, Hooper et al. (2004) found no effect of omega-3 fatty acids on total cardiovascular events (fatal and non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular disease, sudden death and non-scheduled cardiovascular interventions). Neither of this estimates seem applicable for the risk assessment model, since conclusion of Hooper and co-workers is based on heterogenous data whereas the estimate of Caroll and co-work seems over-optimistic compared to the results of the other meta-analyses.

Recently published JELIS study (Yokoyama et al. 2007) among hypercholesterolemic subjects in Japan has not been included in the meta-analyses. JELIS study recruited also subjects with no history of coronary artery disease and therefore provided valuable new

information for the effect of fish oils in primary prevention. Treatment group of JELIS study consumed 1.8 g of EPA supplements/ day and had a significant 19 % reduction in major coronary events compared to control group. In sub-group analysis for primary prevention, risk reduction was 18%, but not statistically significant.

Furthermore, fish is a significant source of selenium. In observational studies blood or toe nail selenium concentrations have been inversely associated with coronary heart disease risk. However, a recent meta-analysis (Flores-Mateo et al. 2006) concluded that the validity of this association is uncertain as data from randomized trials has been inconclusive and further data from large ongoing trials is needed to understand the role of selenium in the cardiovascular disease. Due to these uncertainties, no dose-responses are presented for selenium and cardiovascular disease outcomes.

Coronary heart disease and myocardial infarction

International Society for the Study of Fatty Acids and Lipids has recommended a minimum 500 mg combined intake of EPA and DHA for cardiovascular health (Drevon et al. 2004). All the reviewed meta-analyses (Guallar Castillon et al. 1993, He et al. 2004a, Whelton et al. 2004 and König et al. 2005) came to conclusion that fish consumption reduces the risk of coronary heart disease mortality among general population. The meta-analysis of König et al. (2005) is proposed to be used in the benefit-risk assessment model as it gives dose-response figures for both fish and marine omega-3 fatty acids. Furthermore the 17 % reduction in coronary heart disease mortality by one to four servings of fish/ month with additional reduction of 3.9 % by each additional serving/ week as presented by König et al. (2005) is well in line with the other meta-analyses.

According to meta-analysis of König et al. (2005) small quantities of fish consumption (at least one portion/ month) were associated with risk reductions in nonfatal MI risk by 27%, but additional fish consumption conferred no incremental benefits. The other reviewed meta-analyses did not provide feasible estimates for the effect of fish or omega-3 fatty acids and risk of fatal or non-fatal myocardial infarction in general population. This is because the meta-analyses have not assessed deaths due myocardial infarction, but due to more general indication i.e. coronary heart disease.

Two original publications provide interesting supplementary data on the effect of fish and EPA consumption on the risk of myocardial infarction. In the Chigaco Western Electric study (Davigulus et al. 1995) the men who consumed 35 g or more of fish daily as compared with the non-consumers, the relative risk of any death from myocardial infarction was 0.56 (95 % CI: 0.33, 0.93) with a statistically significant trend also with lower doses. In the recent JELIS study (Yokoyama et al. 2007) subjects using EPA supplement and with no history of coronary artery disease had hazard ratio of 0.79 (95 % CI: 0.52, 1.19) for fatal and non-fatal myocardial infarction compared to controls.

Meta-analysis for secondary prevention of cardiovascular disease indicates a 20 % risk reduction of nonfatal myocardial infarction and 30 % reduction for fatal myocardial infarction and sudden death for subjects consuming additional marine omega-3 fatty acids (Bucher et al. 2005). No dose-response was presented in the meta-analysis. If looking at the original pooled studies, the lowest effective doses were at least two servings of fatty fish/ week or about 500 mg of EPA/ day.

Stroke (ischemic and hemorrhagic)

Both Bouzan et al. (2005) and He et al. (2004b) present dose-responses for fish consumption and risk of stroke. Their results are well in line with each other and the figures presented by Bouzan appear to be in form that can be easily transferred into mathematical formula. He et al. (2004) also postulated that evidence for the beneficial effects is particularly for ischemic stroke whereas for hemorrhagic stroke, which is less common type of stroke, the evidence remains equivocal.

Risk factors of cardiovascular disease

Meta-analyses provide applicable dose-responses data for the effects of fish oils on serum triglycerides (Balk et al. 2006), blood pressure (Morris et al. 1993) and heart rate (Mozaffarian et al. 2005) among general population. However, at individual level, to achieve a clinically meaningful change in biomarkers, fish oil is needed in doses that are higher than what is gained through habitual fish consumption. No meta-analyses have been conducted on the effect of fish consumption on these risk markers.

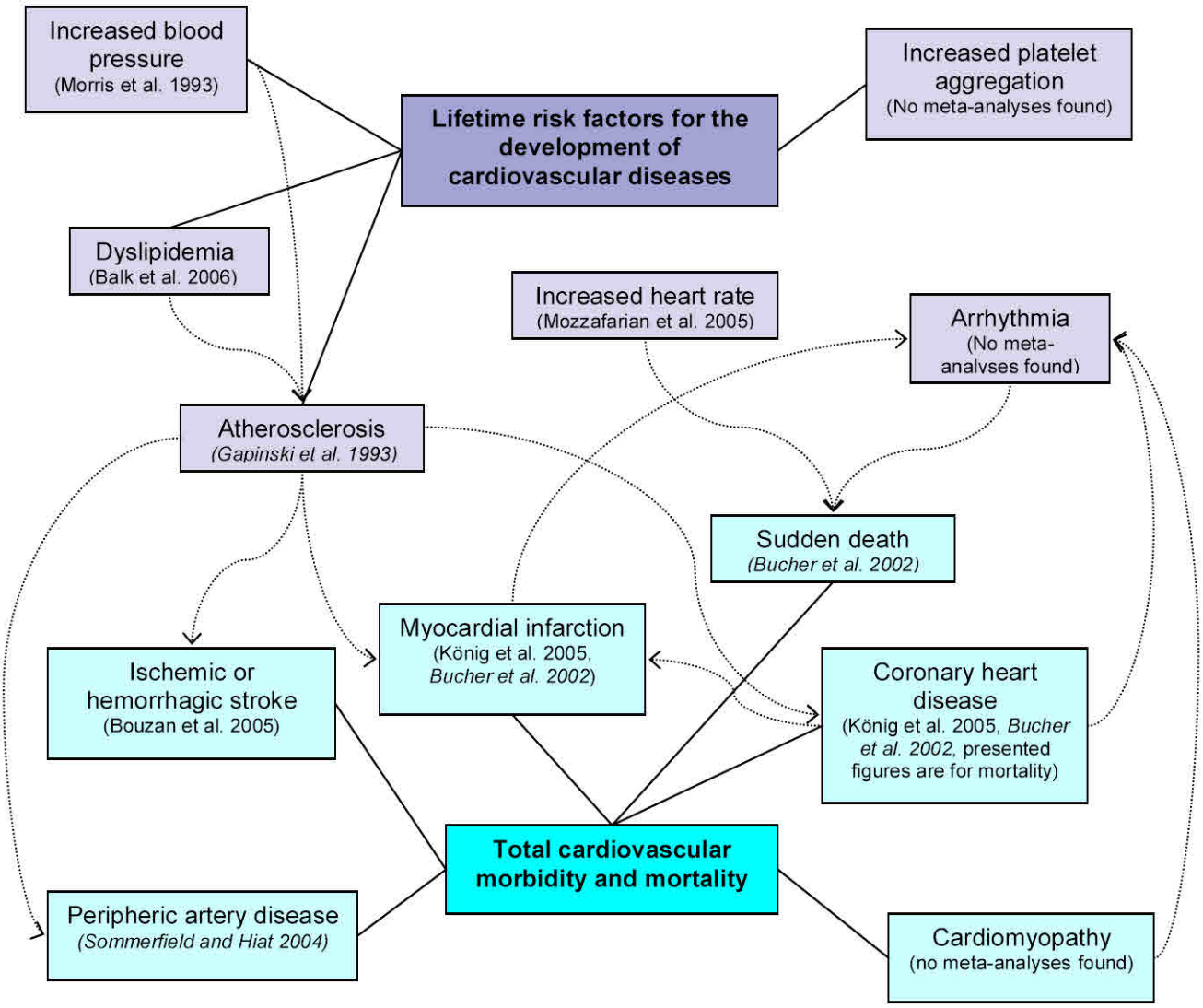

Figure 1. Simplified illustration on the cardiovascular disease outcomes (blue boxes) and risk factors for the cardiovascular diseases (violet boxes) of interest for the cardiovascular effects of fish or omega-3 fatty acids. Dotted arrows represent causal relationships of increased risk. The life time risk factors affect various disease end points, but to keep the figure readable, all causality arrows are not drawn in the picture. Key references containing applicable dose-response data are given in brackets, in which normal text refers for general population and *italics* for secondary prevention.

Conclusion

Several cardiovascular health benefits have of fish consumption have been quantified for general adult population. A dose-response relationship can be presented for fish consumption and decreased risk of stroke, non-fatal myocardial infarction, coronary heart disease mortality and even overall mortality. In addition to this there is quantified data that in secondary prevention abundant use of fish or fish oil supplementation reduce the risk of sudden death and death from myocardial infarction. However, no single estimate for overall cardiovascular morbidity and mortality with applicable dose-response was found. Major reason for this is that the protective effect appears to be stronger for fatal myocardial infarction and sudden death than for non-fatal cardiovascular events.

There is insufficient dose-response data on cardiovascular disease outcomes for children and adolescents. Therefore the only way to assess the effects is through risk marker data.

Table 1. Dose-responses between fish or its constituents and various **cardiovascular health end points** with the applicability of the available dose-response data in different population subgroups.

Reference	Children	Adults (Primary prevention)	Adults (Secondary prevention)	Elderly (Primary prevention)	Elderly (Secondary prevention)	Presented dose response
Total mortality and mortality to overall cardiovascular events						
Hooper et al. 2004	-	+	+	+	+	In pooled analysis of RCT's, no reduction in the risk of **total mortality** (relative risk 0.98, 95% CI; 0.70, 1.36) or **combined cardiovascular events** (relative risk 1.09, 95% CI; 0.87, 1.37) was found in those taking additional omega-3 fatty acids (studies with high risk of bias were excluded from the analysis). Respectively, in cohort studies relative risks were 0.65, 95% CI; 0.48, 0.88 for total mortality and 0.91, 95% CI; 0.73, 1.3 (with significant statistical heterogeneity) for combined cardiovascular events. The meta-analysis presents risk ratios for several cardiovascular end points, but without readily available data on examined doses. Therefore this meta-analysis provides no quantified data that could be directly used for the benefit-risk assessment. It is of importance to notice, that the original data is from studies with omega 3 fatty acids from both vegetable and/ or marine origin. Furthermore studies for primary and secondary prevention were also analyzed together.
Yzebe et al. 2004	-	-	+	-	+	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% CI; 0.76, 0.94) and the incidence of **death due to MI** by 24% (relative risk 0.76, 95 % CI; 0.66, 0.88).
Mozaffarian and Rimm 2006	-	+	+	+	+	Modest consumption of fish (eg, 1-2 servings/wk), reduces risk of **coronary death** by 36% (95% CI, 20%-50%; P<.001) and **total mortality** by 17% (95% confidence interval, 0%-32%; P = .046) and may favourably affect other clinical outcomes. Intake of 250 mg/d of EPA and DHA appears sufficient for primary prevention.
Carroll et al. 2002	-	+	+	+	+	Omega-3 fatty acids (1-2 servings of fish/ week or EPA/ DHA supplements 850 mg/day) 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%. (No actual meta-analysis conducted).
Wang et al. 2006	-	+	+	+	+	No dose –responses given but the reviewers concluded that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of alpha-linolenic acid, reduces the rates of **all-cause mortality**, **cardiac and sudden death**, and possibly **stroke**. The evidence for the benefits of fish oil is stronger in secondary- than in primary-prevention settings.
Coronary heart disease (CHD) and ischemic heart disease (IHD) mortality, sudden death or fatal and nonfatal myocardial infarction						
Bucher et al. 2002	-	-	+	-	+	The risk ratio of patients who were on n-3 polyunsaturated fatty acid-enriched diets compared with control diets or placebo was • 0.8 (95% CI 0.5 to 1.2, P = 0.16; Breslow-Day test for heterogeneity, P = 0.01) for **nonfatal myocardial infarction** • 0.7 (95% CI 0.6 to 0.8, P <0.001; heterogeneity P >0.20) for **fatal myocardial infarction** • 0.7 (95% CI: 0.6 to 0.9, P <0.01; heterogeneity P >0.20) for **sudden death**

						No dose-response presented, meta-analysis combines studies with fish and plant derived omega-3 fatty acids. For fish derived omega-3 doses range from 200-400 g of fish/ week to 5.4 g of EPA with 3.6 g of DHA/day.
Konig et al. 2005	-	+	+	+	+	For general population, consuming small quantities of fish is associated with a 17% (95 % CI, 25 % to 9 %) reduction in **CHD mortality** risk, with each additional serving per week associated with a further reduction in this risk of 3.9% (95 % CI, 6.6 % to 0.1 %). One fish serving/ week was estimated to correspond 0.14 g/d of marine omega-3 fatty acids. For general population, small quantities of fish consumption (at least one portion/ month) were associated with risk reductions in **nonfatal MI** risk by 27% (95 % CI, 34 % to 21 %), but additional fish consumption conferred no incremental benefits. For secondary prevention there is insufficient data to draw conclusions on the effects of fish consumption on CHD as studies have been conducted with fish oil supplements, in which daily intake of omega-3 fatty acids greatly exceeds what may be gained via fish consumption.
He et al. 2004 a	-	+	-	+	-	In the general population each 20 g/ day increase in fish intake has been related to 7 % lower risk for **CHD mortality** i.e. the pooled RR for CHD mortality has been estimated to be 0.93 (95 % CI, 0.87 to 0.99, p for trend=0.03).
Whelton et al. 2004	-	+	-	+	-	In general population fish consumption (about 36 g/ day or 2.2 servings/ week) vs. little to no fish consumption has been associated with a relative risk of • 0.83 (95% confidence interval 0.76 to 0.90; p <0.005) for **fatal CHD** • 0.86 (95% confidence interval 0.81 to 0.92; p <0.005) for **total CHD**
Guallar Castillon et al. 1993	-	+	+	+	+	Cohort studies indicate for general population, that relative risk for **ischemic heart disease** mortality with an intake of 30 g/day of fish compared to no intake was 0.96 (95% CI: 0.93-1.00; P = 0.058). A single clinical trial conducted among post-myocardial infarction patients indicates for secondary prevention, that an intake of 200-400 g/week of fatty fish **reduces total mortality** by 29% (relative risk of intake compared to no intake 0.71; 95% CI: 0.54-0.93)
Incidence of stroke						
Bouzan et al. 2005	-	+	-	+	-	In general population any fish consumption confers substantial relative risk reduction for **stroke** compared to no fish consumption (12% for the linear model, 95% CI -25 %, 1 %), with the possibility that additional consumption confers incremental benefits (central estimate of 2.0% per serving per week, 95 % CI -6.6 %, 2.7 %).
He et al. 2004 b	-	+	-	+	-	In general population compared to those who never consumed fish or ate fish less than once per month, the pooled RRs for **total stroke** were • 0.91 (95% CI, 0.79 to 1.06) for individuals with fish intake 1 to 3 times per month • 0.87 (95% CI, 0.77 to 0.98) for once per week • 0.82 (95% CI, 0.72 to 0.94) for 2 to 4 times per week • 0.69 (95% CI, 0.54 to 0.88) for > or =5 times per week (P for trend=0.06)

Table 2. Dose-responses between fish or its constituents and various **risk markers** of cardiovascular disease with the applicability of the dose-response data in different population subgroups.

Reference	Children	Adults (Primary prevention)	Adults (Secondary prevention)	Elderly (Primary prevention)	Elderly (Secondary prevention)	Presented dose response
Restenosis following percutaneous transluminal coronary angioplasty						
Gapinski et al. 1993	-	-	+	-	+	Patients undergone percutaneous transluminal coronary angioplasty and using marine omega-3 fatty acids (at doses of about 4-5 g/ day) have 13.9% (95% confidence interval [CI], 3.2% to 24.5%) **lower restenosis rates** compared to controls
Heart rate						
Mozaffarian et al. 2005	?	+	+	+	+	In general population fish oil supplementation (0.8-15 g/ d) **decreased heart rate** by 1.6 bpm (95% CI, 0.6 to 2.5; P=0.002) compared with placebo. Decrease is greater among individuals with initially higher heart rate.
Blood pressure						
Geleijnse et al. 2002	?	+	+	+	+	High intake of fish oil through supplements (median dose in studies 3.7 g/ day) may **lower blood pressure**, especially in older and hypertensive subjects. The antihypertensive effect of lower doses of fish oil (< 0.5 g/day) however, remains to be established.
Morris et al. 1993	?	+	+	+	+	Dose-response effect of fish oil on **blood pressure** of -0.66/-0.35 mm Hg/ g omega-3 fatty acids.
Appel et al. 1993	?	+	+	+	+	Fish oil doses higher than 3 g/ day can lead to clinically relevant **blood pressure reductions** in individuals with untreated hypertension
Serum lipids and other serum risk markers of cardiovascular disease						
Balk et al. 2006	?	+	+	+	+	Each increase in fish oil dose of 1g/ day is associated with a **decrease in triglyserides** of 8 mg/dL (0.09 mmol/l).
Peripheric artery disease						
Sommerfield and Hiatt 2004	-	-	+	-	+	No applicable dose-response effect found

References

Appel LJ, Miller ER 3rd, Seidler AJ, Whelton PK: Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. Arch Intern Med. 1993;153(12):1429-38.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J: Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189(1):19-30.

Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Konig A, Lawrence RS, Savitz DA, Teutsch SM: A quantitative analysis of fish consumption and stroke risk. Am J Prev Med. 2005;29(4):347-52.

Bucher HC, Hengstler P, Schindler C, Meier G: N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2002;112(4):298-304.

Carroll DN, Roth MT.: Evidence for the cardioprotective effects of omega-3 Fatty acids. Ann Pharmacother. 2002 Dec;36(12):1950-6

Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB: Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med. 1997;336(15):1046-53.

Din JN, Newby DE, Flapan AD: Omega 3 fatty acids and cardiovascular disease--fishing for a natural treatment. BMJ. 2004;328(7430):30-5.

Drevon CA, Harris B, Sinclair A, Spector A: Recommendations for intake of polyunsaturated fatty acids in health adults. ISFALL (International Society for the Study of Fatty Acids and Lipids) Newsletter 2004;11(2):12-25.

Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E: Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr. 2006;84(4):762-73

Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS: Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. Arch Intern Med. 1993;153(13):1595-601.

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ: Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002 Aug;20(8):1493-9.

GISSI-Prevenzione investigators: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999;354(9177):447-55.

Gochfeld M, Burger J: Good fish/bad fish: a composite benefit-risk by dose curve. Neurotoxicology. 2005;26(4):511-20.

Guallar Castillon E, Jimenez Jimenez FJ, Tafalla Garcia M, Martin-Moreno JM: [Fish consumption and coronary mortality in the general population: a meta-analysis of cohort studies] Gac Sanit. 1993 Sep-Oct;7(38):228-36. Spanish. (Abstract)

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P: Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004;109(22):2705-11. a

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P: Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke. 2004;35(7):1538-42.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Moore H, Worthington HV, Durrington PN, Ness AR, Capps NE, Davey Smith G, Riemersma RA, Ebrahim SB: Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database Syst Rev. 2004;(4):CD003177.

Konig A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM: A quantitative analysis of fish consumption and coronary heart disease mortality. Am J Prev Med. 2005;29(4):335-46.

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F; GISSI-Prevenzione Investigators: Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105(16):1897-903.

Morris MC, Sacks F, Rosner B: Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation. 1993;88(2):523-33.

Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB: Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. Circulation. 2005;112(13):1945-52.

Mozaffarian D, Rimm EB: Fish intake, contaminant and human health. JAMA 2006;296(15):1885-1899.

Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Akerblom HK, Viikari JS: Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003;290(17):2277-83

Sommerfield T, Hiatt WR: Omega-3 fatty acids for intermittent coudication. Cohrane database of systematic reviews 200, Issue 1. Art. No.:CD003833.DOI: 10.1002/14651858.CD003833.pub2.

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006;84(1):5-17.

Whelton SP, He J, Whelton PK, Muntner P: Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol. 2004;93(9):1119-23.

Yzebe D, Lievre M: Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. Fundam Clin Pharmacol. 2004;18(5):581-92. (Abstract)

APPENDIX 1

Meta-analyses and selected reviews on cardiovascular effects of omega-3 fatty acids and fish consumption. Blue text highlights the studied substance, red the effect of interest and green the type of studies on which the meta-analysis has been conducted.

Study	Objective and data	Main results	Conclusions by reviewers
Total mortality and mortality to overall cardiovascular events			
Hooper et al. 2004	Random effects meta-analysis on the effects of **dietary or supplemental omega 3 fatty acids on total mortality, cardiovascular events** or cancers including 48 **randomized controlled trials** (36,913 participants) and 41 **cohorts**.	Pooled trial results did not show a reduction in the risk of total mortality or combined cardiovascular events in those taking additional omega 3 fats (with significant statistical heterogeneity). Sensitivity analysis, retaining only studies at low risk of bias, reduced heterogeneity and again suggested no significant effect of omega 3 fats. Restricting analysis to trials increasing fish-based omega 3 fats, or those increasing short chain omega 3s, did not suggest significant effects on mortality or cardiovascular events in either group. Subgroup analysis by dietary advice or supplementation, baseline risk of CVD or omega 3 dose suggested no clear effects of these factors on primary outcomes.	It is not clear that dietary or supplemental omega 3 fats alter total mortality, combined cardiovascular events or cancers in people with, or at high risk of, cardiovascular disease or in the general population. There is no evidence we should advise people to stop taking rich sources of omega 3 fats, but further high quality trials are needed to confirm suggestions of a protective effect of omega 3 fats on cardiovascular health. There is no clear evidence that omega 3 fats differ in effectiveness according to fish or plant sources, dietary or supplemental sources, dose or presence of placebo.
Yzebe et al. 2004	Meta-analysis of **trials** (**10 RCTs** with altogether 14,727 patients) regarding the efficacy of **omega-3 fatty acids in preventing cardiovascular mortality and morbidity** among adults with recent or acute myocardial infarction (MI), or angina. Five relevant outcomes, mortality from all causes, fatal and non-fatal MI, non-fatal stroke and angina, were measured.	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.
Mozaffarian and Rimm 2006	Benefit-risk analysis on the health effects of fish including effects of **EPA and DHA** on **coronary death and total mortality in prospective cohorts and RCT's**	Modest consumption of fish (eg, 1-2 servings/wk), especially species higher in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduces risk of coronary death by 36% (95% confidence interval, 20%-50%; P<.001) and total mortality by 17% (95% confidence interval, 0%-32%; P = .046) and may favourably affect other clinical outcomes. Intake of 250 mg/d of EPA and DHA appears sufficient for primary prevention.	For major health outcomes among adults the benefits of fish intake exceed the potential risks.

Carroll et al. 2002	Review of **epidemiologic and clinical trial data** on **cardiovascular effects of marine-derived omega-3 fatty acids** and evaluation of their benefits in the prevention of coronary heart disease.	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.	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.
Wang et al. 2006	Systematic review on the effects of **n-3 FAs** (consumed as fish or fish oils rich in eicosapentaenoic acid and docosahexaenoic acid or as alpha-linolenic acid) **on cardiovascular disease outcomes** **RCT and observational studies** that were of at least 1 y in duration and that reported estimates of fish or n-3 FA intakes and cardiovascular disease outcomes	Secondary prevention was addressed in 14 randomized controlled trials (RCTs) of fish-oil supplements or of diets high in n-3 FAs and in 1 prospective cohort study. Most trials reported that fish oil significantly reduced all-cause mortality, myocardial infarction, cardiac and sudden death, or stroke. Primary prevention of cardiovascular disease was reported in 1 RCT (with alpha-linolenic acid supplementation of 10 ml/day), in 25 prospective cohort studies, and in 7 case-control studies. No significant effect on overall deaths was reported in 3 RCTs that evaluated the effects of fish oil in patients with implantable cardioverter defibrillators. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. The effects on stroke were inconsistent.	Increased consumption of n-3 FAs from fish or fish-oil supplements, but not of alpha-linolenic acid, reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke. The evidence for the benefits of fish oil is stronger in secondary- than in primary-prevention settings. Adverse effects appear to be minor.
Coronary heart disease (CHD) and ischemic heart disease (IHD) mortality, sudden death or fatal and nonfatal myocardial infarction			
Bucher et al. 2002	Meta-analysis on the effects of **dietary and non-dietary (supplemental) intake of n-3 polyunsaturated fatty acids** on **coronary heart disease** in **randomized controlled trials** (11 trials, which included 7951 patients in the intervention and 7855 patients in the control groups)	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.	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.

Konig et al. 2005	Development of a dose-response relationship between **fish consumption on coronary heart disease (CHD) mortality and nonfatal myocardial infarction (MI)**. **Eight studies** were identified (29 exposure groups).		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.
He et al. 2004 a	Meta-analysis of **cohort studies** on the association between **fish intake** and **CHD mortality**. 11 eligible studies and 13 cohorts, including 222 364 individuals with an average 11.8 years of follow-up. A linear regression analysis of the log RR weighted by the inverse of variance was performed to assess the possible dose-response relation	Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 (95% CI, 0.79 to 1.01) for fish intake 1 to 3 times per month, 0.85 (95% CI, 0.76 to 0.96) for once per week, 0.77 (95% CI, 0.66 to 0.89) for 2 to 4 times per week, and 0.62 (95% CI, 0.46 to 0.82) for 5 or more times per week. Each 20-g/d increase in fish intake was related to a 7% lower risk of CHD mortality (P for trend=0.03).	Fish consumption is inversely associated with fatal CHD. Mortality from CHD may be reduced by eating fish once per week or more.
Whelton et al. 2004	Meta-analysis on association of **fish consumption** with **fatal and total CHD** in **observational studies** (14 cohort and 5 case-control)	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.	Fish consumption is associated with a significantly lower risk of fatal and total CHD and may therefore be an important component of lifestyle modification for the prevention of CHD.
Guallar Castillon et al. 1993	Meta-analysis on **fish intake** and **ischemic heart disease mortality** in the general population based on five **cohort studies** The total number of participants in these studies was 27,656, with an average follow-up in each study between 7.5 and 25 years and a total of 1,731 coronary deaths.	The combined estimate of the relative risk for an intake of 30 g/day of fish compared to no intake was 0.96 (95% CI: 0.93-1.00; P = 0.058). Due to the presence of statistically significant heterogeneity among the studies, unexplained by a priori factors, we combined the studies assuming a random effects model, obtaining a relative risk estimate of **0.92 (95% CI: 0.84-1.01; P = 0.090)**.	These results, together with the results of the only clinical trial of fish intake performed in post-myocardial infarction patients, in which an intake of 200-400 g/week of fatty fish reduced total mortality by 29% (relative risk of intake compared to no intake 0.71; 95% CI: 0.54-0.93), suggest a moderate beneficial effect of fish intake on coronary mortality.
Incidence of stroke			
Bouzan et al. 2005	Development of a dose-response relationship between **fish consumption** and **stroke risk.** Six **observational studies**, including five prospective cohorts and one case-control study (total of 24 exposure groups).		Any fish consumption confers substantial relative risk reduction compared to no fish consumption (12% for the linear model), with the possibility that additional consumption confers incremental benefits (central estimate of 2.0% per serving per week).
He et al. 2004 b	Meta-analysis on **fish intake** and **incidence of stroke** in **cohort studies** (9 independent cohorts from 8 studies).	Compared with those who never consumed fish or ate fish less than once per month, the pooled RRs for total stroke were 0.91 (95% CI, 0.79 to 1.06) for individuals with fish intake 1 to 3 times per month, 0.87 (95% CI, 0.77 to 0.98) for once per week, 0.82 (95% CI, 0.72 to 0.94) for 2 to 4 times per week, and 0.69 (95% CI, 0.54 to 0.88) for > or =5 times per week (P for trend=0.06).	Intake of fish is inversely related to risk of stroke, particularly ischemic stroke. Fish consumption as seldom as 1 to 3 times per month may protect against the incidence of ischemic stroke.

	In stratified analyses of 3 large cohort studies with data on stroke subtypes, the pooled RRs across 5 categories of fish intake were 1.0, 0.69 (95% CI, 0.48 to 0.99), 0.68 (95% CI, 0.52 to 0.88), 0.66 (95% CI, 0.51 to 0.87), and 0.65 (95% CI, 0.46 to 0.93) for ischemic stroke (P for trend=0.24); and 1.0, 1.47 (95% CI, 0.81 to 2.69), 1.21 (95% CI, 0.78 to 1.85), 0.89 (95% CI, 0.56 to 1.40), and 0.80 (95% CI, 0.44 to 1.47) for hemorrhagic stroke (P for trend=0.31).

References

Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Konig A, Lawrence RS, Savitz DA, Teutsch SM: A quantitative analysis of fish consumption and stroke risk. Am J Prev Med. 2005;29(4):347-52.

Bucher HC, Hengstler P, Schindler C, Meier G: N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med. 2002;112(4):298-304.

Carroll DN, Roth MT.: Evidence for the cardioprotective effects of omega-3 Fatty acids. Ann Pharmacother. 2002 Dec;36(12):1950-6

Guallar Castillon E, Jimenez Jimenez FJ, Tafalla Garcia M, Martin-Moreno JM: [Fish consumption and coronary mortality in the general population: a meta-analysis of cohort studies] Gac Sanit. 1993 Sep-Oct;7(38):228-36. Spanish. (Abstract)

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P: Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. Circulation. 2004;109(22):2705-11. a

He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P: Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke. 2004;35(7):1538-42.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Moore H, Worthington HV, Durrington PN, Ness AR, Capps NE, Davey Smith G, Riemersma RA, Ebrahim SB: Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database Syst Rev. 2004;(4):CD003177.

Konig A, Bouzan C, Cohen JT, Connor WE, Kris-Etherton PM, Gray GM, Lawrence RS, Savitz DA, Teutsch SM: A quantitative analysis of fish consumption and coronary heart disease mortality. Am J Prev Med. 2005;29(4):335-46.

Mozaffarian D, Rimm EB: Fish intake, contaminant and human health. JAMA 2006;296(15):1885-1899.

Wang C, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. Am J Clin Nutr. 2006;84(1):5-17.

Whelton SP, He J, Whelton PK, Muntner P: Meta-analysis of observational studies on fish intake and coronary heart disease. Am J Cardiol. 2004;93(9):1119-23.

Yzebe D, Lievre M: Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. Fundam Clin Pharmacol. 2004;18(5):581-92. (Abstract)

APPENDIX 2

Examples of meta-analyses and systematic reviews on cardiovascular risk markers and omega-3 fatty acids or fish consumption. Blue text highlights the studied substance, red the effect of interest and green the type of studies on which the meta-analysis has been conducted.

Study	Objective and data	Main results	Conclusions by reviewers
Restenosis following percutaneous transluminal coronary angioplasty			
Gapinski et al. 1993	Meta-analysis on the effect of **omega-3 fatty acids** on rate of **restenosis following percutaneous transluminal coronary angioplasty** in **RCT's**.	For four studies that used angiography to define coronary restenosis, the absolute difference in restenosis rates between treatment and control groups was 13.9% (95% confidence interval [CI], 3.2% to 24.5%). Furthermore, regression analysis revealed a positive linear relationship between the dose of omega-3 fatty acids used and the absolute difference in restenosis rates ($r = .99$, $P < .03$). When three studies that used stress testing as a means of determining restenosis rates were added to the four studies that used angiography, the risk difference was 5.1% (95% CI, -3.8% to 13.9%).	Restenosis after coronary angioplasty is reduced by supplemental fish oils, and the extent of the observed benefit may be dependent on the dose of omega-3 fatty acids used.
Heart rate			
Mozaffarian et al. 2005	Meta-analysis of 30 **randomized, double-blind, placebo-controlled trials** on the effect of **fish oil** on **heart rate (HR),** a major risk factor for sudden death	In the overall pooled estimate, fish oil decreased HR by 1.6 bpm (95% CI, 0.6 to 2.5; P=0.002) compared with placebo. Between-trial heterogeneity was evident (Q test, P<0.001). Fish oil reduced HR by 2.5 bpm (P<0.001) in trials with baseline HR > or =69 bpm (median) but had little effect (0.04-bpm reduction; P=0.56) in trials with baseline HR <69 bpm (P for interaction=0.03). Fish oil reduced HR by 2.5 bpm (P<0.001) in trials with duration > or =12 weeks but had less effect (0.7-bpm reduction; P=0.27) in trials with duration <12 weeks (P for interaction=0.07). HR reduction with fish oil intake did not significantly vary by fish oil dose (range, 0.81 to 15 g/d), type of HR measure, population age, population health, parallel versus crossover design, type of control oil, or study quality by Delphi criteria (P for interaction >0.25 for each).	In randomized controlled trials in humans, fish oil reduces HR, particularly in those with higher baseline HR or longer treatment duration. These findings provide firm evidence that fish oil consumption directly or indirectly affects cardiac electrophysiology in humans. Potential mechanisms such as effects on the sinus node, ventricular efficiency, or autonomic function deserve further investigation.

Blood pressure			
Geleijnse et al. 2002	Metaregression analysis on the **antihypertensive effect** of **fish oil** A total of 36 **trials** (50 strata) included, 22 of which had a double-blind design.	Intake of fish oil was high in most trials (median dose: 3.7 g/day). Fish oil reduced systolic BP by 2.1 mmHg [95% confidence interval (CI): 1.0, 3.2; P < 0.01] and diastolic BP by 1.6 mmHg (95% CI: 1.0. 2.2; P < 0.01). Restricting the analysis to double-blind trials yielded BP reductions of 1.7 mmHg (95% CI: 0.3, 3.1) and 1.5 mmHg (95% CI: 0.6, 2.3), respectively. BP effects tended to be larger in populations that were older (> 45 years) and in hypertensive populations (BP >or= 140/90 mmHg).	High intake of fish oil may lower BP, especially in older and hypertensive subjects. The antihypertensive effect of lower doses of fish oil (< 0.5 g/day) however, remains to be established.
Morris et al. 1993	Meta-analysis of 31 **placebo-controlled trials** on 1356 subjects on effect of **omega-3 fatty acids in fish oil** on **blood pressure**	The mean reduction in blood pressure caused by fish oil for the 31 studies was -3.0/-1.5 mm Hg (95% confidence intervals: systolic blood pressure: -4.5, -1.5; diastolic blood pressure: -2.2, -0.8). There was a statistically significant dose-response effect when studies were grouped by omega-3 fatty acid dose: -1.3/-0.7 mm Hg at doses < or = 3 g/d, -2.9/-1.6 mm Hg at 3.3 to 7 g/d, and -8.1/-5.8 mm Hg at 15 g/d. Both eicosapentaenoic acid and docosahexaenoic acid were significantly related to blood pressure response. There was no effect on blood pressure in eight studies of "healthy" persons (mean reduction, -0.4/-0.7 mm Hg) at an overall mean dose of 4.2 g omega-3 fatty acids/d. By contrast, there was a significant effect of -3.4/-2.0 mm Hg in the group of hypertensive studies with a mean fish oil dose of 5.6 g/d and on systolic blood pressure only in six studies of hypercholesterolemic patients (-4.4/-1.1 mm Hg) with a mean dose of 4.0 g/d. A nonsignificant decrease in blood pressure was observed in four studies of patients with atherosclerotic cardiovascular disease (-6.3/-2.9 mm Hg). Variations in the length of treatment (from 3 to 24 weeks), type of placebo, and study design (crossover or parallel groups) did not appear to account for inconsistent findings among studies.	There is a dose-response effect of fish oil on blood pressure of -0.66/-0.35 mm Hg/g omega-3 fatty acids. The hypotensive effect may be strongest in hypertensive subjects and those with clinical atherosclerotic disease or hypercholesterolemia.
Appel et al. 1993	Meta-analysis of 17 **controlled clinical trials** on **omega-3 PUFA supplementation** and **blood pressure.**	In the 11 trials that enrolled normotensive individuals (n = 728), omega-3 PUFA supplementation led to significant reductions of systolic BP (SBP) and diastolic BP (DBP) in two and one trials, respectively. In the six studies that enrolled untreated hypertensives (n = 291), significant reductions of SBP and DBP were present in two and four trials, respectively. Weighted, pooled estimates of SBP and DBP change (mm Hg) with 95% confidence intervals were -1.0 (-2.0 to 0.0) and -0.5 (-1.2 to +0.2) in the trials of normotensives,	Diet supplementation with a relatively high dose of omega-3 PUFA, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension. However, use of omega-3 PUFA as antihypertensive therapy will require demonstration of long-term efficacy and patient acceptability of lower doses

		and -5.5 (-8.1 to -2.9) and -3.5 (-5.0 to -2.1) in the trials of untreated hypertensives. In 13 of 17 studies, trial duration was less than 3 months. Doses of omega-3 PUFA tended to be high (average dose > 3 g/d in 11 trials). The magnitude of BP reduction was greatest at high BP but was not significantly associated with dose of omega-3 PUFA. Side effects, most commonly eructation and a fishy taste, occurred more frequently in omega-3 PUFA participants than in control participants (28% vs 13%, P < .001).	
Serum lipids and other serum risk markers of cardiovascular disease			
Balk et al. 2006	Systematic review of 21 **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.
Peripheric artery disease			
Sommerfield and Hiatt 2004	Review on the effects of **omega-3 fatty acids** for **intermittent claudication** in **four randomized controlled trials**	Omega-3 fatty acids reduce triglyseride levels in subjects with intermittent cloudication.	Omega-3 fatty acids appear to have some beneficial biochemical and hemodynamic effects in people with intermittent claudication but there is no evidence of improved clinical outcomes

References

Appel LJ, Miller ER 3rd, Seidler AJ, Whelton PK: Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. Arch Intern Med. 1993;153(12):1429-38.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J: Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006;189(1):19-30.

Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS: Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. Arch Intern Med. 1993;153(13):1595-601.

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ: Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002 Aug;20(8):1493-9.

Morris MC, Sacks F, Rosner B: Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation. 1993;88(2):523-33.

Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB: Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. Circulation. 2005;112(13):1945-52.

Sommerfield T, Hiatt WR: Omega-3 fatty acids for intermittent coudication. Cohrane database of systematic reviews 200, Issue 1. Art. No.:CD003833.DOI: 10.1002/14651858.CD003833.pub2.

APPENDIX 3

References for selection original studies of interest

Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC: Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med. 1995;332(15):977-82.

Daviglus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB: Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med. 1997;336(15):1046-53.

Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, Kark JD, Riemersma RA, Martin-Moreno JM, Kok FJ; Heavy Metals and Myocardial Infarction Study Group: Mercury, fish oils, and the risk of myocardial infarction. N Engl J Med. 2002;347(22):1747-54.

Guallar E, Hennekens CH, Sacks FM, Willett WC, Stampfer MJ: A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. J Am Coll Cardiol. 1995;25(2):387-94.

Guallar E, Aro A, Jimenez FJ, Martin-Moreno JM, Salminen I, van't Veer P, Kardinaal AF, Gomez-Aracena J, Martin BC, Kohlmeier L, Kark JD, Mazaev VP, Ringstad J, Guillen J, Riemersma RA, Huttunen JK, Thamm M, Kok FJ: Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study. Arterioscler Thromb Vasc Biol. 1999;19(4):1111-8.

GISSI-Prevenzione investigators: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999;354(9177):447-55.

Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE: Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA. 2002;287(14):1815-21.

Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC: Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr. 2000;72(4):912-21.

Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group: 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. Circulation. 2006;113(2):195-202

Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D; Fatty Acid Antiarrhythmia Trial Investigators: Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. Circulation. 2005;112(18):2762-8.

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F; GISSI-Prevenzione Investigators: Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002;105(16):1897-903.

Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Marti A, Martinez JA, Martin-Moreno JM: Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score. Eur J Nutr. 2002;41(4):153-60.

Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH: Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. Am J Epidemiol. 1995;142(2):166-75.

Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML: The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART).Eur J Clin Nutr. 200256(6):512-8.

Sasazuki S; Fukuoka Heart Study Group: Case-control study of nonfatal myocardial infarction in relation to selected foods in Japanese men and women. Jpn Circ J. 2001;65(3):200-6.

Tavani A, Pelucchi C, Negri E, Bertuzzi M, La Vecchia C: n-3 Polyunsaturated fatty acids, fish, and nonfatal acute myocardial infarction. Circulation. 2001;104(19):2269-72.

Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K; Japan EPA lipid intervention study (JELIS) Investigators: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369(9567):1090-8.

Yuan JM, Ross RK, Gao YT, Yu MC: Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. Am J Epidemiol. 2001;154(9):809-16.