EPA/DHA Omega-3 Fatty Acids in the Primary and Secondary Prevention of Cardiovascular Disease and the Modification of Risk Factors

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Numerous epidemiological and controlled-intervention trials in apparently healthy individuals have supported highly beneficial effects of EPA (eicosapentaenoic acid) plus DHA (docosahexaenoic acid) from fish and fish oils in decreasing cardiac mortality and the favourable modification of numerous risk factors for cardiovascular disease (CVD) independent of blood cholesterol-lowering (Holub, 2002). A review of various cohort studies (on over 200,000 subjects combined with a 12-13 year follow-up) indicated an overall 23% and 38% reduction in CHD mortality for those consuming 2-4 servings/week and ≥ 5/week, respectively (He *et al.,* 2004). The corresponding reduction in stroke mortality was 18% and 31%, respectively (He *et al.,* 2004). Two servings per week would provide approximately 250 mg of (EPA/DHA) daily on average while five fish servings per week would be expected to provide approximately 650-750 mg EPA plus DHA daily. The Multiple Risk Factor Intervention Trial in the U.S. indicated that increasing intakes of EPA/DHA (up to 665 mg/day) from fish over 10.5 years were associated with a markedly reduced risk of cardiac-related mortality (Dolecek, 1992).

The numerous mechanisms for the cardioprotective effects of EPA/DHA as reviewed (Holub, 2002; Balk *et al.,* 2005) include anti-thrombotic effects and other favourable effects on the haemostatic system, reduction in malignant ventricular arrhythmias (via enrichment of cardiac lipids in omega-3 fatty acids), improved endothelial relaxation, inhibitory effects on atherosclerosis and inflammation (altered eicosanoid synthesis, suppressed production of inflammatory cytokines, etc), and blood

triglyceride-lowering in the fasted and postprandial state independent of cholesterol-lowering. Elevated fasting triglyceride levels in the circulation have become better recognized as an important risk factor for cardiovascular disease and associated outcomes including myocardial infarctions. However, the conventional cut-off level in the public health care system often employs levels of 150 mg/100 mL (1.7 mmol/L) or more which appears not to fully protect the population. The relationship between fasting blood serum triglyceride levels and the risk for fatal plus non-fatal cardiovascular disease and indicates that even fasting triglyceride levels below the conventional cut-off impose a significant increased risk for cardiac-related outcomes (Onat *et al.,* 2006). Three grams of EPA + DHA per day typically result in reductions in fasting triglyceride levels of 25-30% within a 3-4 week period (Harris, 1997). These reductions are also realized in a high proportion of patients who are being maintained on pharmaceutical treatment (with statins) for cholesterol reduction (Holub, 2007). A recent systematic review and meta-analysis has confirmed the consistent and clinically-significant dose-dependent reduction of fasting blood triglyceride levels independent of any lowering in LDL-cholesterol levels (Eslick *et al.,* 2009). Modest intakes of DHA/EPA (1000- 1252 mg/day for 8 weeks) have shown (Schwellenbach *et al.,* 2006) significant triglyceride- lowering (18-22%) in those with fasting triglyceride levels greater than 200 mg/dL (2.25 mmol/L). Clinical reports have also indicated that EPA/DHA supplementation enhanced the stability of atherosclerotic plaques (Thies *et al.*, 2003), reduced the induction of ventricular tachycardia (Schrepf *et al.*, 2004), moderately reduced the resting heart rate (Stark and Holub, 2004), and provided favourable cardiac autonomic changes (Holguin *et al.,* 2005).

Very recently, data from the U.S. National Center for Health Statistics on lifestyle-related preventable causes of death estimated that insufficient intakes of EPA/DHA omega-3 fatty acid from seafood were responsible for approximately 72,000 – 96,000 preventable deaths per year in the United States (Danaei *et al.*, 2009).

Numerous review articles (including meta-analyses) as published in peer-reviewed journals during the past few years have all provided strong evidence in support of the beneficial effects of supplemental intake of EPA/DHA from fish oil in both primary- and secondary- prevention studies (Bucher *et al.,* 2002; Studer *et al.,* 2005; Harper and Jacobson, 2005; Wang *et al.,* 2006; O'Keefe *et al.*, 2009; Lavie *et al.,* 2009; He, 2009; Marik *et al.,* 2009; Hill *et al.,* 2009; von Schacky, 2009). In contrast to the various/recent aforementioned reviews and meta-analyses, the systematic review by Hooper *et al.* (2006) of randomized controlled trials (individuals with or without risk factors for CVD) and cohort studies yielded moderate overall relative risks for total mortality of 0.86 and 0.93 for cardiovascular events with higher intakes of long-chain omega-3 (EPA/DHA).

Risk reduction of 30% overall for fatal myocardial infarction and sudden cardiac death and 20% for overall mortality were found to be similar for higher omega-3 intakes from tradiational dietary or non-dietary interventions (Bucher *et al.*, 2002). In a subsequent review of 6 fish oil trails wherein daily doses of (EPA/DHA) ranging from 270 mg – 4800 mg daily were provided over 12 – 42 months to those with coronary heart disease (CHD) or having risk factors for CVD, an overall reduction in sudden death and total mortality was demomstrated without a significant reduction in nonfatal myocardial infarction (Harper and Jacobson, 2005). A recently-published review (Hill *et al.*, 2009)

has concluded that, for prevention, fish oil from fish or supplements can further decrease CVD risk over and above prudent dietary advice alone. In another recent review, it was concluded that there is little doubt that the long-chain omega-3 fatty acids in fish are the key nutrients responsible for the benefits in CVD prevention (He, 2009). Further, individuals at risk for CVD who do not consume fish are advised to consider taking fish oil supplements.

The GISSI-Prevenzione trial from Italy (GISSI-Prevenzione Investigators, 1999) on 11,324 patients who had experienced a myocardial infarction indicated that, in the presence of a Mediterranean-type diet as well as treatment with various cardiovascular medications, those patients receiving approximately 900 mg/day of EPA/DHA over the subsequent 3.5 years exhibited a marked reduction in overall cardiovascular death and a 45% reduction in sudden cardiac death. Recently, the potential benefits of omega-3 fatty acid supplementation providing 1800 mg of EPA per day relative to a placebo (control) supplementation was studied in over 18,000 hypercholesterolemic patients who were being treated with statins for elevated blood cholesterol levels but were free of known CHD (Yokoyama *et al.,* 2007). The patients were followed for an average duration of 4.6 years and major coronary events were measured. The risk for major coronary events (including sudden cardiac death plus fatal/nonfatal myocardial infarction plus other nonfatal events including nonstable angina, angioplasty, stenting, and bypass surgery) were found to be reduced by approximately 20% in all patients including those with a history of coronary artery disease. When investigating sub-sets of patients within the total group, these Japanese investigators reported that very dramatic reductions in the cumulative incidence of major coronary events was particularly observed within those

patients having elevated fasting triglyceride levels (equal or greater than 150 mg/100 mL) along with lower HDL-cholesterol levels (less than 40 mg/100mL). In this sub-set of patients, EPA supplementation appeared to provide a 53% reduction in major coronary events as compared to the control group not receiving such supplementation (Saito *et al.,* 2008).

Albert and colleagues (2002) conducted a prospective study amongst healthy males who were followed for up to 17 years in the Physicians' Health Study at the Brigham Women's Hospital and the Harvard School of Public Health in Boston. Baseline measurements of omega-3 levels in blood samples were correlated with the subsequent risk of sudden cardiac death. A progressively lower relative risk of sudden death was observed in those individuals with correspondingly higher levels of omega-3 fatty acids in their blood samples. Those with the highest levels of omega-3 fatty acids in their circulating blood (6.1-10.2% of total fatty acids) had approximately $1/10^{th}$ the risk of sudden death as compared to those subjects with much lower blood levels of omega-3 fatty acids (2.1-4.3% of total fatty acids).

For the general population, the position paper of the American Dietetic Association and the Dietitians of Canada as published (Kris-Etherton and Innis, 2007) recommended a daily intake of 500 mg (EPA/DHA). The recently-published recommendation form the Technical Committee of the International Life Sciences Institute North America towards establishing a DRI for (EPA/DHA) advised a nutritionally-achievable intake of 250 – 500 mg/day for overall cardioprotection (Harris *et al.*, 2009). The recent review by Lavie *et al.* (2009) advocated a target intake of at least 500 mg (EPA/DHA) daily for primary prevention for individuals without CVD. In their

dietary guidelines, the American Heart Association advises a daily intake of 900 mg (EPA/DHA) from fish oil or via fish oil supplementation in those with coronary disease (Krauss *et al.,* 2000).

It is noteworthy that typical Japanese intakes of (EPA/DHA) of 900-1500 mg daily from several servings of fish/ seafood (Kobayashi *et al.*, 2001) have been reported which contrasts with daily North American intake of only 120-150 mg (EPA/DHA) daily (Holub, 2002).

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