Management of IHD

B. Secondary Prevention

The role of omega-3 fatty acids

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CHD is the major cause of premature death in the western world; it is important source of disability and contributes in large part to the escalating costs of health care. The underlying pathology is usually atherosclerosis, which develop insidiously over many years and usually advanced by the time symptoms occur. Myocardial infarction (MI) is a complication of coronary heart disease (CHD). Death and MI nevertheless frequently occur suddenly and before medical care is available, and many therapeutic interventions are therefore inapplicable or palliative. CHD is a preventable disease. The mass occurrence of CHD relates to lifestyles and modifiable physiological factors. Risk factor modifications have been unequivocally shown to reduce mortality and morbidity, especially in people with either unrecognized or recognized CHD.

Recently it has become clear that in addition to risk factors such as overweight, lack of exercise, smoking, hypertension and hypercholesterolemia, psychological factors play a key role for prognosis in patients with MI. Depression, anxiety, perceived social support and social desirability may have an effect on mortality and morbidity in such patients. Therefore, there is high medical need for drugs which lower the incidence of sudden death and have an effect on other risk factors such as depression.

During the last decades progress has been made in the treatment of patients who survived MI. The introduction of aspirin, thrombolytics, β-blockers, ACE-inhibitors and statins led to reduction in both short-term and immediate mortality rates among patients suffering from MI. Nevertheless, patients who survive an acute MI are at high risk, with life expectancy half that of their peers who have not experienced similar events, and with increased risk for subsequent cardiovascular events and death. The risk of sudden cardiac death (SCD) increases with the severity of systolic dysfunction after MI. Sudden death has proved to be difficult to treat than coronary heart disease.

In addition, when one considers that sudden arrhythmic death accounts for at least 25% of all cardiovascular death, it is striking that none of the agents currently recommended for post-MI care has clear anti-arrhythmic activity. There are currently no anti-arrhythmic therapies available for survivors of MI that can be routinely recommended[1].

Amiodarone has been extensively tested and is widely accepted to be a potent anti-arrhythmic agent. Results of large clinical trials in survivors of MI, such as CAMIAT and EMIAT, have not shown a clear benefit of this agent[2].

Because of the significant toxicity associated with this drug and the lack of consistent reductions in mortality, amiodarone is not recommended routinely in survivors of MI. Recently the Sudden Cardiac Death in Heart Failure Trial (SCDHFT)[3] convincingly showed that Amiodarone does not reduced mortality in patients at high risk for sudden death. Membrane active agents that reduce the risk of ventricular fibrillation (VF) in the animal laboratory have also proved to be ineffective and even dangerous in patients[4].

The use of ICD reduces mortality in many high risk patients, but the recent results of the Defibrillators in Acute Myocardial Infarction Trial (DINAMIT)[5] clearly showed that in post-MI patients the usual benefit seen with the ICD does not occur. This is likely due to the fact that most common mechanism of arrhythmic death in these patients is VF due to ischaemia which is different from sustained ventricular tachycardia (VT) typically occurring in heart failure or in the very late phase (several years) after MI. There is therefore a need for well-tolerated safe therapies which reduce the risk of sudden death after recent MI.

The preventative role of omega-3 fatty acids

Epidemiological evidence of benefit

The evidence that omega-3 fatty acids are beneficial in the prevention of complications of cardiovascular disease first came from epidemiological observations. This is perhaps first assumed by the British physiologist Hugh Sinclair in the early 1940s, who stated that the possibility of deficiency in some fatty acids might account for the rise in Western diseases such as CHD. In 1944 he undertook his first visit to Greenland, were he noted the 'Eskimos' freedom from any trace of arcus senile and their liability for epistaxix. His view was set out in a letter to the Lancet in 1956 'Deficiency of essential fatty acids and atherosclerosis, etcetera'[6]. The fact that Greenland Eskimos had a low mortality rate from CHD despite a high intake of fat in their diet (about 40% of calories) – the so called 'Eskimos paradox' – led to a series of epidemiological studies in the late 1970s by the Danish investigators Bang and Dyerberg[7]. Indeed, their analysis suggested a close correlation between the observed low incidence of CHD among the Inuit and high consumption of fish-eating mammals (including seal, walrus, whale) that are rich in omega-3 fatty acids) which are scarce or absent in land animals and plants. They found that Inuit's intake of saturated fat was low (9% of total calories), whereas the dietary intake of omega-3 fatty acids was high (4.2% of total calories). Such observation contrasted with the much higher rates of CHD in the Danes whose diet had a comparable amount of total fat (42% of total calories) but a much lower intake of omega-3 fatty acids (<1% of total calories) and much higher intake of saturated fat (22% of total calories)[8].

Therefore these epidemiological studies in the seventies have put forward that dietary rather than genetic factors are responsible for the lower incidence of ischaemic heart disease in Greenland Inuit and have generated a large body of both in vitro and in vivo

experimental studies, exploring the putative favorable effects of fish (oil) on atherogenesis and its risk factors.

Studies like the US physician's Health Study reported a 52% decrease in SCD in subject who ate fish at least once per week[9]. There was no decrease in MI, and no incremental benefit seen with greater fish consumption. In the Nurses Health Study[10] dietary consumption of fish and follow-up clinical outcome data from validated questionnaires performed over a 14-year period were compared from 84,688 female nurses, aged 34-59 years. The purpose of the study was to examine the relationship between fish and omega-3 fatty acids consumption and the risk of coronary artery disease. There was a strong inverse relationship between fish consumption and coronary heart disease events, even after adjustment for multiple co-varieties such as age, body mass index, smoking, etc. (Figure 1). In the thirty-year follow-up of the Chicago Western Electric Study, men who consumed high quantities of fish had almost a 40% lower risk of death from coronary heart disease than men who consumed no fish at all[11]. In the Zutphen study, Kromhout et al showed that mortality from coronary heart disease was more than 50% lower among those who consumed at lease 30 gm of fish per day than among those who did not eat fish[12].

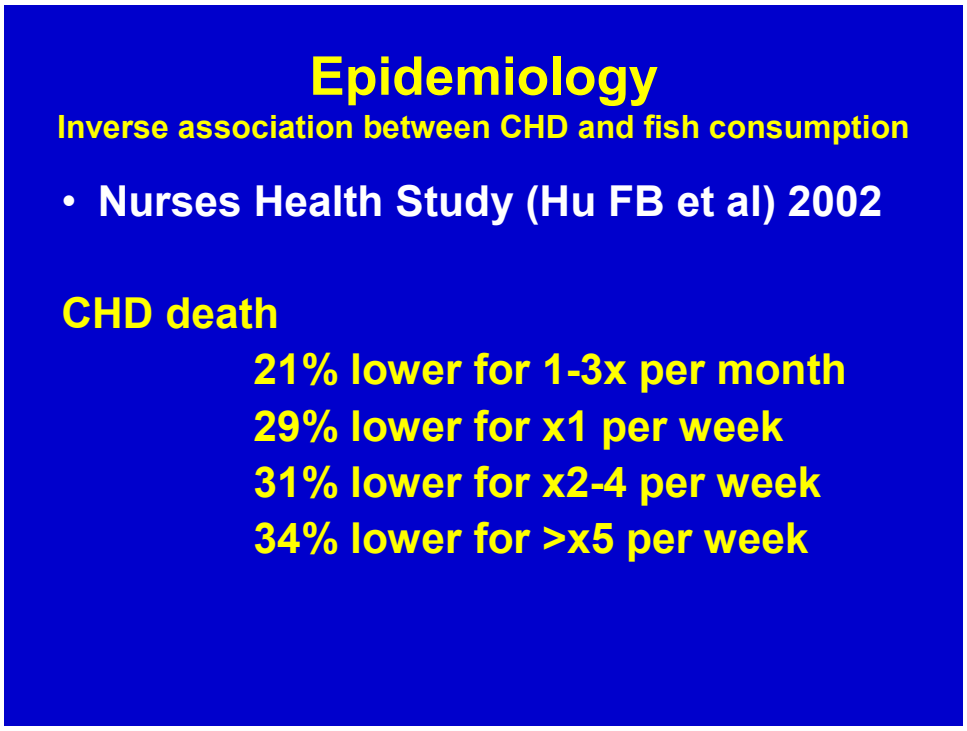

Figure 1: Nurses Health Study by *Hu FB et al 2002*[10]

A recent meta-analysis[13] of epidemiological studies was performed to examine the relationship between fish intake and coronary heart mortality. This analysis included data from over 200 000 individuals with an average follow-up of 11.8 years. Compared to

people who never ate fish or ate less than once per month, this study reported significantly reduced relative risks for coronary mortality were 0.89 for fish intake of 1-3 times per month, 0.77 for fish intake of 2-4 times per week and 0.62 for fish intake of 5 or more times per week. Each 20 g per day increase in fish intake resulted in a 7% lower risk of coronary heart disease mortality (p=0.03).

In conclusion, most epidemiological studies have supported a clear association between fish intake and reduced mortality from cardiovascular disease. The overwhelming consensus of experts is that a strong association between dietary intakes of omega-3 fatty acids and reduced coronary mortality exists[14].

What are Omega (n-3) fatty acids?

Fatty acids are saturated, monounsaturated, or polyunsaturated. The two important groups of polyunsaturated fatty acids (PUFAs) are the omega-6 and the omega-3 fatty acids. The omega-6 fatty acids are available mainly from vegetable oils. There are three principal omega-3 fatty acids: alpha-linolenic acid is available from certain plants but eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are primarily obtained from marine sources. Omega-3 fatty acids are long chain PUFAs with the first of the many double bonds at the third carbon atom (methyl end). In the UK, α-linolenic acid is the primary source of omega-3 fatty acids, but humans have only a limited ability to elongate the lipid chain to form EPA and DHA. The best dietary source of these omega-3 fatty acids is fish (Table 1).

Fish-based omega-3 PUFAs consist of EPA and DHA. These fatty acids form an important part of the structural components of the phospholipid membrane of tissues throughout the body, especially rich in the myocardium, retina, brain, and spermatozoa[15].

	EPA/DHA per 100g
Cod	0.25
Haddock	0.16
Herring	1.31
Kippers	2.59
Mackerel	1.93
Salmon	2.20
Salmon (canned in brine)	1.55
Trout	1.15
Sardines (canned in tomato sauce)	1.67
Pilchards	2.60
Crab (canned)	1.00

Table 1: EPA/DHA Content of Selected Seafoods

- Potential mechanism by which Omega-3 fatty acids may reduce risk for CVD
    - Reduce susceptibility of the heart to ventricular arrhythmia
    - Anti-thrombogenic
    - Hypotriglyceridaemic (fasting and post-prandial)
    - Retard growth of atherosclerotic plaque
        - Reduce adhesion molecule expression
        - Reduce platelet-derived growth factor
        - Anti-inflammatory
- Promote nitric oxide-induced endothelial relaxation
- Mildly hypotensive[3]

Table 2: Potentially cardioprotective effects of omega-3 fatty acids

Potential mechanisms

Although the weight of evidence supports a protective effect of omega-3 fatty acids on coronary heart disease, the mechanisms through which they confer these benefits remain unclear. Omega-3 fatty acids have several potentially cardioprotective effects (Table 2); however, the relative contribution of each of these is not fully understood.

The rapidity of onset of the beneficial effects seen in clinical studies suggest that omega-3 fatty acids might have a membrane stabilizing property, thereby preventing ventricular arrhythmias, hence sudden cardiac death. Reduced heart rate variability (HRV) is a risk predictor for cardiac arrhythmia and sudden cardiac death in patients with prior MI.

Interestingly, intake of omega-3 fatty acids has been shown to positively correlate with increased HRV in dose-dependent manner both in healthy men and in patients with prior MI[16].

Evidence for efficacy in secondary prevention

A growing body of evidence from epidemiological and clinical trials shows that omega-3 fatty acids supplementation and fish consumption are of benefit in the prevention of CHD especially sudden cardiac death. This has considerable implications from the public health perspective. Three secondary prevention trials have demonstrated the benefit of fish oil or supplementation of omega-3 fatty acids. The Diet and Re-infarction Trial (DART)[17] was designed to test the effects of changes in fat, fish and fibre intakes on death and myocardial re-infarction. A randomised, factorial design, controlled trial involved 2033 male patients (mean age 56 years) who survived, with a mean interval of 41 days post MI. The dietary interventions were reduced fat of 30 per cent of total calories, increased polyunsaturated/ saturated (P/S) ratio to 1: (two portions of fatty fish – 200-400g weekly) and increased cereal fibre to 18mg/day. The primary endpoints were

total mortality and CHD events (deaths + non-fatal MI) after a follow-up for 2 years. Patients intolerant to fish were given a fish oil supplement 3g/day. The results showed that total mortality was significantly reduced in the fish advice group 94 (9.3 per cent) vs 130 (12.8 per cent) (29 per cent), $p<0.05$. CHD deaths were 78 (7.7 per cent) vs 116 (11.4 per cent) $p<0.01$. The benefit was seen within 4 months. No effect was seen on non-fatal events. No benefit from fat and fibre advice was observed.

In a second study[18], 360 post-MI patients received fish oil (EPA 1.08g/day), mustard oil, (α-linolenic acid, 2.9g/day) or placebo. After 1 year total cardiac events were 24.5 per cent, 28 per cent and 34.7 per cent, ($p<0.01$)in the three groups respectively.

A large trial was needed to answer questions arising from epidemiological data and small intervention trials. This was provided by the GISSI-Prevenzione trial published in 1999[19]. The study involved 11 324 recent (<3 months) MI survivors (1665 women). It was a multicentre, randomised, open label comparison of Omacor (1g/day), vitamin E (300mg/day), both of these two supplements or none. The study lasted 3.5 years and the primary composite endpoints were death, non-fatal MI and stroke. Baseline therapy was comparable to secondary prevention trials: 92 per cent anti-platelet drugs, 47 per cent ACE inhibitors, 44 per cent beta-blockers, 5 per cent of patients on lipid lowering drugs.

The dietary habits and secondary preventative treatments were well balanced across all four groups. The groups' dietary habits were recorded: >1 serving of fish a week; >1 serving of fruit a day; >1 serving of vegetables a day; regular olive oil. All groups were well balanced for all these habits at baseline (average 73.2 per cent; 80.3 per cent; 39.7 per cent and 73.6 per cent respectively) and the numbers with these dietary habits increased during the course of the trial (average 87.6 per cent; 88 per cent; 54.6 per cent; 82.5 per cent at 42 months respectively).

The groups were also well balanced with respect to patients undergoing revascularization procedures at baseline, six months and 48 months. At the beginning of this trial an average of 4.7 per cent of patients were taking a cholesterol lowering drug (statins); this had increased to 28.6 per cent after 6 months and to 45.5 per cent after 42 months.

The results indicated that treatment with fish oil (Omacor), but not vitamin E significantly lowered the risk of the primary endpoint. Relative risk reduction in primary endpoint: 10 per cent (95 per cent CI 1-18) by two-way analysis; 15 per cent (2-26) by four-way analysis. Risk reduction in individual endpoints: 14 per cent in death (3-24) by 2-way analysis,
20 per cent by four-way analysis, cardiovascular death 17 per cent (3-29) by 2-way analysis, 30 per cent (13-44) by four-way. No effect on non-fatal MI. Sudden death was reduced by 45 per cent ($p=0.01$).

A follow up analysis by Marchioli et al[20], assessed the early effect of Omacor. The results showed an early divergence at 3 months (p=0.037) with a reduction in total mortality of 41 per cent and sudden death of 53 per cent at 3 months (p=0.048).

The GISSI-P trial was the biggest to use omega-3 fatty acids and the first to use such a high concentration of EPA and DHA in 1g single capsule.

A recent trial of 3114 men with angina unexpectedly found that individuals advised to eat oily fish, and particularly those given fish oil capsules, had a higher risk of cardiac death than people not given advice to eat fish (11.5 per cent vs 9 per cent, p=0.02).[21]

Population	Recommendation
Patients without Documented CHD	Eat a variety of fish, (preferably oily) twice a week. Include foods rich in alpha-linolenic acid
Patients with Documented CHD	Consume =1g of EPA+DHA per day preferably from oily fish. Supplementation could be considered in consultation with the physician
Patients needing Triglyceride lowering	2-4g EPA+DHA per day provided as capsules under a physicians care.

The investigators speculated that this may have arisen from risk compensation or other changes in patients' behavior. Several flaws in this study weakened the validity of the results, and they should be viewed with caution until more evidence becomes available. For more discussion of this trial please see below.

In addition Mozaffarian et al[22] analysed the risk of 5201 men and women older than 65 years from the Medicare eligibility lists and found that consumption of tuna or broiled or baked fish was associated with lower incidence of atrial fibrillation (AF). Similarly, Calo et al[23] reported a reduction of post operative AF by 54.4% in 160 randomized patients after CABG.

This clear evidence was reflected in the European Society of Cardiology (ESC) guidelines for the prevention of sudden death[24,25]; omega-3 fatty acids (EPA & DHA)

were rated as a class IIa, level of evidence B recommendation for the secondary prevention of sudden death after MI.

Remarkably, the relative risk reduction (RR) for total mortality was 0.7 for EPA/DHA, 0.83 for ACE-inhibitors and 0.77 for β-blockers. For sudden cardiac death it was an impressive relative risk reduction of 0.55 for EPA/DHA, whereas it was only 0.80 for ACE-inhibitors and 0.74 for β -blockers.

Three recently published smaller ICD trials, in situation different from acute post-MI situation in GISSI-Prevenzione, examined patients who had a defibrillator implanted for the incidence of arrhythmic events. Raitt et al[26], in a possibly underpowered study of 200 randomized patients, could not demonstrate a reduction of incidences of ventricular tachycardia and only a trend for less episodes of ventricular fibrillation. Leaf et al[27] could show in a secondary outcome analysis that fish oil prevented ventricular arrhythmic events more effectively than olive oil but missed this point in the primary outcome analysis. The SOFA-trial by Brouwer et al[28], when compared fish oil vs. placebo in a similar ICD setting with 273 patients, only showed a trend but note a significant benefit. Remarkably, Burr et al[21] in recent study examining the effect of the advice to increase fish oil consumption in patients with angina, showed a lack of benefit under these circumstances. All these latter quasi-neutral studies share the following common deficiencies: they lack the measurement of EPA & DHA in the trial population. So in the case of the last mentioned study by Burr et al[21] we do not know whether patients really followed the advice to increase fish consumption or not, since compliance was not measured. And in the 3 ICD studies one should be aware of the fact that they involved only 4 percent of the study population of the Gissi-Prevenzione trial in a situation not analogous to the acute post-MI situation. Rupp al[29,30] hypothesize that this may be due to the fact that in acute infarction free EPA & DHA are raised in advance to levels required for their anti-arrhythmogenic action by the event and sympathetic drive, whereas the ICD is expected to terminate re-entrant ventricular tachycardias or ventricular fibrillation before a marked sympathetic activation and release of EPA & DHA occurs.

Connolly and Healy[31], when reviewing the data on the protective effect of omega-3 PUFAs on cardiovascular deaths, underline the recommendations of the AHA & ESC and come to the conclusion that the benefit of secondary and probably of primary prevention of n-3 PUFAs is based primarily on avoiding episodes of sudden cardiac death.

The non-membrane bound EPA+DHA level and MI

The major sources for the release of EPA & DHA are phospholipid membranes. EPA, DHA and arachidonic acid are incorporated to a greater extent into the inner position of membrane phospholipids[32]. A rise in sympathetic nervous system activity is associated with a raised phospholipase A2 activity and the subsequent release of fatty acids is expected. This has been shown for pigs after coronary occlusion, which had been fed a diet enriched in EPA & DHA triacylglycerols[33]. Compared with pigs fed saturated fat, an over-proportional increase of the EPA & DHA concentration was observed in the raised myocardial free fatty acids. The relevance of non-membrane bound EPA & DHA is

demonstrated also in a study on dogs which has sustained a prior MI[34]. The animals were tested during treadmill exercise and occlusion of the left circumflex artery. When 50-60 minutes prior to coronary occlusion, a 70% omega-3 fatty acids concentrate was administered intravenously, ventricular fibrillation did not occur. A similar infusion of soy bean oil emulsion resulted as expected in prompt development of ventricular fibrillation. Since the 50-60 minutes were too short and the administered amount not enough for raising the whole body membrane EPA & DHA content appreciably, it can be deduced that EPA & DHA present in serum had a protective action[34]. In accordance with this contention would be the finding that sustained ventricular tachycardia can be reduced by infusion of 3.8 g omega-3 marine triacylglycerols in patients with ICDs[35].

Anti-Arrhythmic Effect

Omega-3 fatty acids modify biologic function in many ways[14]. Principally, they enter membrane phospholipids and alter membrane structure and function (Figure 2). Perhaps most importantly they modify the electrical activities of myocytes reducing the tendency for cardiac arrhythmia[36]. They can inhibit synthesis of pro-inflammatory cytokines and they reduce aggregational properties of blood platelets. They have a direct effect on triglyceride synthesis and lower triglyceride levels[37].

In a series of studies, it has been shown by Leaf et al that the free fatty acids of EPA and DHA but not other fatty acids inhibit the Na^+ channel activity which occurs rapidly and can be washed out[38]. In addition, the cardiac Na^+ -Ca^{2+} exchanger[39] and the L-type Ca^{2+} channel[40] which have been inferred particularly in after depolarizations were inhibited. For explaining inhibitory effects also on other channels like the transient outward K^+ current[41] and the major voltage-dependent delayed rectifier current (Kv1.5)[42] one has to infer inhibitory effects which are specific for EPA and DHA but not particular ion channel. Also the Ca^{2+} release from intracellular Ca^{2+} stores, the sarcoplasmic reticulum, was inhibited[42,43]. The inhibitory effects of EPA & DHA have been attributed to the non-covalent incorporation of free fatty acids into the micro-environment of ion channels and ensuring conformational change (38). A consequence of this mechanism is that the critical concentration of free EPA & DHA has to be reached before an adequate number of channels become inhibited and anti-arrhythmogenic effects ensue. After MI, sympathetic activity is increased due to impaired pump performance leading to a rise in myocardial free fatty acids. The release of EPA & DHA is amplified by the preferred release of fatty acids from the inner position of phospholipids by phospholipase A2.

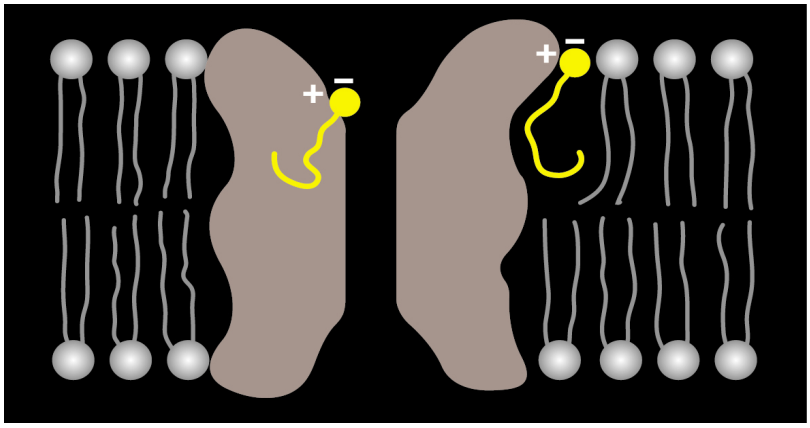

Figure 2:
A working hypothesis for the actions of n-3 PUFAs on ion channels in cardiomyocyte membranes is that the structural or physical chemistry of n-3 PUFAs enables them to occupy sites either in the phospholipid bilayer near to ion channels or within hydrophobic domains of the ion channel proteins themselves. In these positions, the negative charge of the n-3 PUFA carboxyl group can interact with positive charges in the ion channel proteins[44].

It might not be unexpected that protective effects can be smaller in patients with ICD. In contrast to ischaemic events such as MI which raise free EPA & DHA to levels required for their anti-arrhythmogenic action, the ICD is expected to terminate re-entrant ventricular tachycardias or ventricular fibrillation before a marked sympathetic activation and release of EPA & DHA occurs. In the trial by [26]Raitt et al, 1.8 g/day EPA & DHA ethyl esters did not reduce the risk of ventricular tachycardia or fibrillation in 100 patients with ICDs when compared with 100 patients on placebo (olive oil). The study on omega-3 fatty acids and ventricular arrhythmia (SOFA-trial) by Brouwer et al[45] assessed effects of taking 2 g fish oil on life-threatening arrhythmias in ICD patients. At 12 months, 30% of the 273 patients in the fish oil group had experienced either life-threatening arrhythmia or death compared to 33% of the 273 patients in the placebo oil group (not statistically significant). Among the subgroup of 342 patients who previously

had MI there were a trend towards a beneficial effect of fish oil (p=0.086). In this subgroup, 28% of the patients on fish oil experienced either life-threatening arrhythmia or death compared to 35% of patients on placebo oil.

Although the study appears to be underpowered for the subgroup analysis, the trend would be in accordance with the GISSI-Prevenzion study. In the study by Leaf et al[27] 402 ICD patients were randomized to 2.6 g of EPA & DHA or olive as placebo for 12 months. Compliance with the double-blind treatment was similar in the two groups; however, the non-compliance rate was high (35% of all enrolees). This might not be surprising since four 1.0 g capsules had to be taken daily. The primary end-point, time to first ICD event for ventricular tachycardia or fibrillation confirmed by stored ECG or death from any cause was (risk reduction of 28%; p=0.057). For those who stay on protocol for at least 11 months, the anti-arrhythmic benefit of EPA & DHA ethyl esters was improved for those with confirmed events (risk reduction of 38%; p=0.034). In this study capsules with only 65% EPA & DHA instead of 84% as in the case of Omacor which was used in the GISSI-Prevention Trial.

Further support for anti-arrhythmogenic effects of omega-3 fatty acids was provided in the study of Calo et al[23]. Two 1 g capsules of EPA & DHA ethyl esters were administered during hospitalization in patients undergoing coronary artery bypass graft surgery (CABG). Prospective AF developed in 27 patients of the control group (33.3%) and in 12 patients of the EPA & DHA group (15.2%) (p=0.13). There was no significant difference in the incidence of non-fatal post-operative complications, and post-operative mortality was similar in the EPA & DHA treated patient (1.3%) versus controls (2.5%). After CABG, the EPA & DHA treated patients were hospitalized for significantly fewer days than controls (7.3 ±2.1 days vs 8.2 ±2.6 days, p=0.017).

In addition inhibitory effects on ion channels by EPA & DHA, the functional impact of various putative anti-arrhythmogenic mechanisms remains to be examined in greater detail. In particular, contributions arising from an increased heart rate variability[46], an improved post-ischaemic recovery[47] and reduced heart rate[48] require further attention. It remains also an intriguing possibility that the process of adverse dilatation of the heart could be attenuated by EPA & DHA as shown in the pressure overload rat heart. When spontaneously hypertensive rats were treated with fish oil, the degree of left ventricular hyperatrophy was not affected, however, the dilatation of the left ventricle was significantly reduced. Since cardiac dilatation is a major predisposing factor for SCD, it could be inferred from these animal experiments that a reduced adverse geometrical remodelling of the heart contributes to the observed protection of the GISSI-Prevention study.

Dietary fish intake and Mercury contamination

Expert opinion in the dietary field now favours moderate increases in the dietary intakes of plant-derived α-linolenic acid based upon the epidemiologic evidence of reduction in

cardiovascular outcome[14]. Recommendations regarding increased dietary intake of fish have been modulated by concern about the risk of increased exposure to mercury. Mercury is a highly reactive heavy metal which is toxic at all doses. The long-term consequences of exposure to, even low, levels of mercury are poorly understood[49]. Fish intake is a major source of human exposure to mercury.

A recent study showed that increased concentration of mercury in human nail clippings was associated with a risk of increased cardiovascular events[49]. When adipose concentrations of DHA were also accounted for in that analysis, the data suggested that the beneficial effects of the omega=3 PUFAs, DHA, on cardiovascular outcomes were offset by detrimental effects of mercury.

The adverse effects of mercury intake arising from fish might have interfered with protective action of EPA and DHA remains unresolved.

Conclusion

In summary there is strong evidence that increased consumption of omega-3 fatty acids can reduce mortality in patients who have suffered an MI. A protection has been inferred from primary prevention studies based on the intake of fish. Stronger evidence comes from interventional studies with EPA and DHA ethyl ester administration involving post-MI patients[19] and ICD patients[27]. Best characterised is currently the link between a low EPA and DHA level and the risk of SCD. Based on the studies of Albert et al[50] and Siscovick et al[51] demonstrating a markedly reduced risk of SCD in persons who exhibit about 3% more EPA and DHA compared with quartile with the lowest EPA and DHA level, it appears that about 6% blood EPA and DHA represent a target level for prevention of SCD. This target level is based also on Rupp H et al data showing that 1 g/day Omacor raises the EPA and DHA level from 3.5 to 5.7% of total fatty acids. The 1g/day Omacor dose equals the regimen of the GISSI-Prevention study, where the risk of total mortality, cardiovascular mortality and sudden death was significantly reduced[19,52,20]. It appears, however, that an upper limit of EPA and DHA concentrations exists above which further coronary heart disease benefit may not occur[53]. This seems to be the case with the 6.2-7.4% range of EPA and DHA in serum phospholipids since an increase to 10.3% by administering 4 g/day Omacor had no further significant effect on the prognosis of cardiac events despite significant triacyglycerol-lowering[54].

In view of the present evidence, it is suggested to include the determination of fatty acid profile in the list of investigated parameters, particularly in patients after MI. This would strengthen the rationale of therapeutic regimens with EPA and DHA as specified in the current guidelines[14,55]. Rupp et al[29] established a gaschromatic micromethod for analysis of EPA & DHA levels on a routine basis since only 10µl of whole blood are required for the determination of a profile involving more that 35 fatty acids.

Further work is required to assess to what extent the protection associated with a given whole blood EPA and DHA level is influenced by the pathophysiology of sever

arrhythmia disorders. In particular, to what extent differences occurs between re-entry tachyarrhythmias in the absence of sever ischaemic event and tachyarrhythmias arising from MI linked with sympathetic nervous system activation and release of polyunsaturated fatty acids.

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