REVIEW ARTICLE

Marine polyunsaturated fatty acids in heart failure

Are the theoretical benefits matched by the clinical data?

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ABSTRACT

Chronic heart failure (CHF) is a common condition, which despite major advances, is still characterized by high mortality (with sudden arrhythmic death a particular risk), poor quality of life due to exercise intolerance and frequent hospitalizations.

Epidemiological studies suggest that populations with a high intake of marine polyunsaturated fatty acids (PUFAs or fish oils) have low levels of cardiovascular mortality. Animal and human studies of fish oil supplementation have demonstrated improved endothelial function and myocardial relaxation, reduced vascular tone and platelet aggregability, and a stabilization of myocyte excitability by prolongation of the refractory period. Marine PUFAs also have potentially important immune-modulating effects, reducing cytokine production and release, and altering prostaglandin metabolism. Data from patients following acute myocardial infarction have suggested that marine PUFA supplementation may reduce early mortality, mostly by reducing the risk of sudden arrhythmic death. Until recently, data in patients with chronic heart failure was lacking, but the recent publication of the GISSI-HF study, randomizing more than 7000 CHF patients to marine PUFA supplementation or placebo has clarified somewhat the role of these agents. The aim of this article is to review the theoretical benefits of marine PUFAs and to discuss the implications of the GISSI-HF study for the management of patients with CHF.
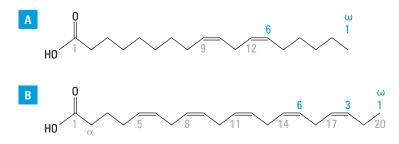
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INTRODUCTION   Despite major advances in medical and device therapies for chronic heart failure (CHF), the syndrome remains a leading cause of death in industrialized countries[1,2], and commonly leads to, or is associated with, medical admissions to hospital.[3,4] In addition, despite optimal therapy, patients suffer persistently poor quality of life.

In the 1940's, Sinclair[5] described the association between a diet high in of marine polyunsaturated fatty acids (PUFAs) and low cardiovascular mortality in an Eskimo population. Since then, fish oils have been under investigation as potential therapy to prevent or treat cardiovascular disease. Studies in patients following acute myocardial infarction suggested a reduction in cardiovascular death with PUFAs.[6,7] The largest of these was the GISSI-Prevenzione study, which compared a combination of 2 fish oils with placebo in more than 11,000 post infarction patients on otherwise conventional treatment. A subanalysis of these data revealed a significant reduction in sudden death by 3 months, (45% >3 years) and a significant reduction in total mortality at 3 months.[8] In patients with cancer cachexia, marine PUFAs can reduce markers of inflammation and lead to weight gain.[9] These data, and previous human and animal work, led to a hypothesis that the syndrome of chronic heart failure, combining myocardial dysfunction, vascular abnormalities, and arrhythmic risk[10], might also be improved by high-dose supplementation with marine PUFAs.[11] The recently reported randomized, placebo-controlled GISSI-HF study set out to explore this theory.

The aim of this article is to discuss the basic and clinical research supporting the use of PUFA

supplementation in CHF patients in order to put the GISSI-HF study into context. We will then critically appraise that study, with the aim of enabling physicians caring for CHF patients to make an informed decision about whether to include PUFAs in their routine practice.

What is a polyunsaturated fatty acid? A fatty acid comprises a long hydrocarbon chain with a single terminal carboxyl group. Combinations of 3 fatty acids bound together with a glycerol molecule make up triglycerides. The specific fatty acids incorporated into such molecules determine whether the fat is solid or liquid at room temperature. Fats are a key source of calories, and the fatty acid constituents are intermediates in the synthesis of phospholipids and eicosanoids (prostaglandins and leukotrienes). Fatty acids have either no double carbon bonds, (known as saturated fatty acids, for example stearic acid), a single carbon double bond, (monounsaturated fatty acids, for example oleic acid) or 2 or more double bonds (polyunsaturated fatty acids such as linoleic acid).

The commonest fatty acids are recognized by their "trivial names", but they are also named by the "ω system". This describes the position of the double bond closest to the terminal carbon, (the furthest from the carboxyl group) the ω carbon. The reason for this is that the ω end of the structure is rarely changed during metabolism (**FIGURE 1**). The major unsaturated fatty acids fall into ω-6 and ω-3 and since mammals cannot synthesize polyunsaturated fatty acids, yet they are important as the base agents in metabolism, hence they are known as "essential" and must therefore be supplied in the diet.

The metabolism of the commonly consumed fatty acids is outlined in **FIGURE 2**. In the typical Western diet, 20–25-fold more ω-6 fats than ω-3 fats are consumed.[12] Linoleic acid (LA), which is present in high concentrations in soy, corn, safflower, and sunflower oils, is the major ω-6 fatty acid. There is a low intake of the ω-3 homologue of LA, α-linolenic acid (ALA), which is present in leafy green vegetables and in flaxseed and canola oils. LA is converted to arachadonic acid (AA) and ALA is converted to eicosapentanoic acid (EPA). The dietary ratios of ω-6 and ω-3 fatty acids determine the cellular ratios of LA and ALA and also the relative quantities of AA and EPA produced. However, synthesis of EPA is limited due to low ALA intake and much of the ω-3 pathway must be supplemented through the diet. The major dietary source of the longer chain ω-3 fatty acids (EPA and docosahexanoic acid (DHA) are fish. Hence these are often called "marine" polyunsaturated fatty acids or "fish oils". During this article, for ease, we will refer to marine fish oils as ω-3 PUFAs (mainly EPA and DHA).

Potential effects of ω-3 PUFAs in chronic heart failure

Due to competition for the cycloxygenase enzyme (COX), the addition of EPA to the cellular environment significantly alters the relative concentrations of the interconversion products, reducing the relative concentrations of the products of AA metabolism.[13-15] This and other features of the fish oils might have multiple effects upon the cardiovascular system. We have focussed specifically on data examining the features of the heart failure syndrome.

Cardiac function and ischemia Fish oils can reduce heart rate[16,17] and improve myocardial relaxation[17,18], possibly contributed to by increased nitric oxide production,[19] and release.[20] EPA and DHA, but not ω-6 fatty acids, protect rat myocardial cells against hypoxia-reoxygenation-induced injury[21], perhaps by inhibiting neutrophil infiltration into infarcted or ischemic myocardium.[22] Despite data suggesting that fish oils can reduce mortality, and improve vascular tone, it is unclear whether fish oils improve subjective or objective markers of myocardial ischemia in patients with stable symptomatic coronary artery disease.[23]

Dysrhythmia Patients with CHF have a high incidence of sudden death.[24] Fish oils have been shown to have an antiarrhythmic effect in vitro and in vivo,[25,26] even when administered acutely[27-30] and they can prevent ischemia-induced ventricular fibrillation.[30] The antiarrhythmic effect is related to their ability to reduce the electrical excitability and automaticity of cardiac myocytes.[27,32] By reducing sodium influx in rat cardiomyocytes[31], they increase the electrical stimulus required to elicit an action potential by approximately 50%, shorten the action potential[32], and prolong the relative refractory time by approximately 150%.[33] By increasing the ratio of EPA to AA within cellular membranes there is an increase in the Ca^{2+}-Mg^{2+}-ATPase activity within myocardial membranes.[34] These cellular alterations reduce the severity of ventricular arrhythmias following the ischemia by altering cardiac sarcoplasmic reticulum Ca-ATPase function, and thereby inhibit the rapid accumulation of intracellular Ca^{2+}[35], reducing the response to noradrenalin, and reducing triggered arrhythmias.[36]
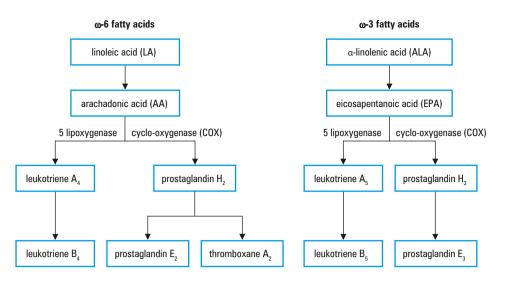
Population studies have suggested that there is an inverse association between blood levels of fish oils and sudden death[37] and ventricular events sensed or treated by implantable cardioverter defibrillators in patients with ischemic heart disease.[38] Secondary prevention trials in myocardial infarction survivors have suggested that high intakes of fish[7] and ALA[39] reduce the incidence of fatal cardiac arrhythmias. In survivors of acute

A
HO... 1 ... 9 ... 12 ... 6 ... ω 1

B
HO... 1 α ... 5 ... 8 ... 11 ... 14 ... 17 ... 6 ... 3 ... ω 1 ... 20

ω-6 fatty acids

linoleic acid (LA) → arachadonic acid (AA) → 5 lipoxygenase → leukotriene A_4 → leukotriene B_4; cyclo-oxygenase (COX) → prostaglandin H_2 → prostaglandin E_2, thromboxane A_2

ω-3 fatty acids

α-linolenic acid (ALA) → eicosapentanoic acid (EPA) → 5 lipoxygenase → leukotriene A_5 → leukotriene B_5; cyclo-oxygenase (COX) → prostaglandin H_3 → prostaglandin E_3

myocardial infarction with left ventricular dysfunction, there was a correlation between platelet DHA, the patients' intake of fish and heart rate variability.[40] In patients with coronary artery disease, fish oil supplementation can reduce the frequency of ventricular extrasystoles[41], and improve heart rate variability.[42,43] Increased dietary intake of marine oils has been linked with a lower incidence of primary cardiac arrest.[44]

Six months of ω-3 PUFA supplementation in patients with dilated cardiomyopathy reduces the risk of malignant arrhythmia.[45]

Despite the impressive and early reductions in sudden death with fish oils in post-infarct patients,[6] there are conflicting data in patients with implantable cardioverter defibrillators (ICD). Three studies have examined this question. In 1 study, daily fish oil supplementation led to non-significant improvements in time to defibrillator discharge and total mortality, but a per-protocol analysis (only 65% patients were taking study medication after 11 months) was required to demonstrate significance.[46] However, 2 further studies in patients with an ICD and prior VT and VF, showed no benefit of 1.8 g and 2 g per day of ω-3 PUFA supplementation.[47,48] A recent meta-analysis combining the 3 trials, including more than 1000 patients with ICDs suggested no overall impact of fish oils on defibrillator discharges.[49]

Vascular resistance Fish oils in relatively high doses can lower blood pressure in patients with hypertension and hypercholesterolemia,[50,51] probably due to changes in the physiochemical properties of cell membranes and reduced vascular tone.[52] Blood pressure lowering seems to be unrelated to sympathetic activity or vascular reactivity to adrenergic neurotransmitters,[53] and is augmented by salt restriction,[54] suggesting an effect on the renin–angiotensin system.[55] Fish oils also increase nitric oxide release.[20]

Renal dysfunction Fish oil supplementation can increase renal blood flow, reduce renal vascular resistance and increase glomerular filtration rate (GFR)[56] possibly due to altered prostaglandin E (PGE) metabolism. Fish oils can preserve renal function and lower blood pressure in heart transplant recipients.[57]

Immune activation Cytokines Cytokine levels are raised in heart failure[58], particularly in those with weight loss[59,60], and higher levels predict a worse prognosis[61]. There is an inverse relation between mononuclear cell EPA content and cytokine production and as cellular EPA concentrations increase cytokine production in monocytes is reduced.[62-65] EPA and DHA also inhibit IL-6 production in human endothelial cells[66] and reduce the concentrations of TNF-α and IL-1β in the arterial wall[67], thereby potentially reducing smooth muscle cell migration and proliferation.[68]

Prostaglandins Prostaglandins are released by inflammatory cells in order to modify the local and systemic inflammatory response and can be either immunostimulatory or immunosuppressive. EPA competitively inhibits AA metabolism by competing for COX enzyme sites (**FIGURE 2**) and can thereby preferentially lead to the formation of prostaglandins of lower pro-inflammatory potency (for example PGE_3) (**FIGURE 2**), and overall to significantly reduced inflammatory prostaglandin production.[69,70] EPA also competes with AA for 5-lipoxygenase leading to the formation of leukotriene B_5 (LTB_5), which has little inflammatory activity compared with LTB_4.[71,72] Thus, increasing dietary fats shifts the balance of the eicosanoids produced to a less inflammatory mixture. However, the formation of PGE itself may be anti-inflammatory suggesting that direct competition may not be the only anti-inflammatory mechanism encouraged by fish oils.[73] There is a theoretical concern that moderate doses of fish oils >2 g per day could affect predominately T-cell responses.[74-76] These changes might put elderly patients with concomitant chronic disease at increased risk of acute infections, but this seems not to have happened.

Cachexia and catabolism Patients with severe CHF often lose weight. This is a consequence

of the inflammatory processes including cytokine production[77,78], reduced calorie intake and increased catabolism.[79] Weight loss or frank cachexia is commonly seen in heart failure[80,81], the prevalence increasing with worsening symptoms.[82,83] Cachexia worsens the prognosis by a factor of 2.6.[82] EPA is effective in attenuating the increased protein catabolism in cancer cachexia[84,85], but this effect has not been investigated in CHF patients.

Rheological abnormalities Patients with CHF are at increased risk of thromboembolism. Ingestion of ω-3 fatty acids leads to suppression of TXA_2 synthesis by platelets and by blood mononuclear cells.[62,86] Decreased platelet aggregation has been demonstrated with EPA supplementation in some[87,88] but not all studies.[89,90] EPA can also reduce the expression of vascular cell adhesion molecule-1 (VCAM-1), endothelial leukocyte adhesion molecule-1 (E-selectin or ELAM-1), and intercellular adhesion molecule-1 (ICAM-1).[91] These adhesion molecules are elevated in CHF and plasma levels are related to the severity of the condition.[92,93] EPA and DHA suppress adherence of monocytes to activated endothelial cells also by affecting endothelial platelet aggregating factor (PAF) generation.[94]

Endothelin 1 Endothelin 1 (ET-1) is a powerful vasoconstrictor[95] and higher levels of ET-1 predict a poor prognosis in CHF patients. EPA suppresses endothelin-1 (ET-1) production in human coronary artery smooth muscle cells.[96]

Clinical trial data (and the GISSI-HF study) The most recent meta-analyses exploring the effects of fish oils in patients with coronary artery disease on all-cause mortality, cardiovascular mortality and arrhythmic death demonstrated that in 11 studies with 32,519 patients there was a significant 20% reduction in death due to cardiac cause, driven mostly by the GISSI-Prevenzione study. All cause mortality was not significantly reduced despite including more than 32,000 patients. None of the studies included in this analysis focussed on or identified patients with heart failure.[97]

The GISSI-HF study enrolled 6975 CHF patients (mean age 67 [11] years) in a four-way stratified design, to rosuvastatin or placebo and 1 g ω-3 PUFA (850–882 mg eicosapentaenoic acid and docosahexaenoic acid) or placebo for a mean follow-up period of 3.9 years.[98] The study population had a mean left ventricular ejection fraction 33 (9)%, and half had ischemic heart disease as the etiology of their heart failure. At baseline, renin-angiotensin-blocking agents were being taken by 94% of patients, and 65% were on β-blockers. The sample size was based upon the rosuvastatin arm, but expected relative mortality reduction attributable to PUFAs was 15% at 3 years based on an assumed absolute mortality of 25%. Hence a population of 7000 patients was predicted to have been suitable to detect a reduction in all-cause mortality with 90% power at a two-sided significance of 0.045. Two primary endpoints were used; time to death and a composite time to death or hospitalization for cardiovascular reasons.

After a mean follow-up of 3.9 years, 955 (27.3%) of patients in the ω-3 PUFA arm and 1014 (29.1%) in the placebo arm had died; adjusted hazard ratio [HR] 0.91 [95.5% CI 0.833–0.998], p = 0.041; unadjusted HR 0.93 (95.5% CI 0.852–1.021); p = 0.124. The Cox proportional hazard model was adjusted for unbalanced variables and the hazard ratio for death due to cardiovascular causes was significant at 0.90 (0.81–0.99); p = 0.045. Absolute risk reduction was 1.8% for all-cause mortality and 2.3% for the combined death and admission for cardiovascular causes. The number needed to treat for 4 years to prevent 1 death was calculated at 56.

Further analyses showed no reduction in mortality due to sudden death, no change in hospitalization for heart failure or ventricular arrhythmias, acute myocardial infarction, or stroke with PUFAs. There were no excess deaths from non-cardiovascular causes. Subgroup analysis of CHF severity, etiology, patient age, and the presence of diabetes did not identify any heterogeneity in outcome. In a per-protocol analysis, those still taking the ω-3 PUFAs at the end of the study had a 3% absolute risk reduction in all cause death (p = 0.004).

Despite the large population, the representative nature of the patients (>40% were >70 years), the completeness of follow-up (only 4 patients were lost over almost 4 years), and the apparent baseline equivalence of the 2 arms, only by adjusting for unbalanced variables, (and it is unclear which variables were adjusted for), were the authors able to demonstrate a reduction in death from cardiovascular causes. They write "Although only adjusting for covariates that are significantly out of baseline balance at p <0.1 is not recommended statistical practice, we did prespecify this approach in the protocol since importantly there is no agreed set of prognostic factors for patients presenting with this type of heart failure." Of note, the groups looked very well-matched at baseline, and it is difficult to see what "adjustment" might have been made.

Comment A positive gloss is put on the study results by the authors who conclude "we have shown that ω-3 PUFA treatment is effective and safe in a large population of patients with heart failure of any cause". A more objective eye would have to conclude that the GISSI-HF study has yielded disappointing results. Any benefits there might be are, at best, very modest.

The lack of clear benefit from ω-3 PUFAs in GISSI-HF is surprising in light of the basic research and the findings of the GISSI-Prevenzione and other non-heart failure studies. The doses of ω-3 PUFA in the 2 GISSI studies were the same, and the fact that the combined arrhythmia studies

are also neutral, despite generally higher daily doses of PUFAs, makes it unlikely that a higher dose would have led to a different result. The size of GISSI-HF allows for sub-group analyses, yet from these there is no hypothesis-generating heterogeneity in outcomes. Patients in NYHA classes II and III, and with ischemic and non-ischemic etiologies had similar non-significant changes, and older patients fared no better than younger ones.

The lack of reduction of sudden death is particularly noticeable. In the GISSI-Prevenzione study it was the reduction in sudden death that drove the overall mortality reduction. It is plausible that the antiarrhythmic effects of PUFAs are greatest during episodes of ischemia, or that they have some direct effect upon ischemia, thereby reducing arrhythmia initiation. Such ischemia-induced arrhythmia is likely to be less common in stable CHF patients than in patients undergoing angioplasty or following acute myocardial infarction, accounting for the weak mortality reduction seen in GISSI-HF. A further possibility is that current medical therapy has achieved all that is likely to be possible for patients with CHF.

Close examination of the survival curves suggests that there might be some separation of the survival curves at about 2 years. This leads to a number of thoughts: that it is too late in the natural history of the disease process to start treatment with PUFAs once the patient has heart failure (which would explain the difference between GISSI-Prevenzione and GISSI-HF); that maybe more prolonged follow up would show a greater effect (and that patients whose life expectancy is less than 2 years should not be burdened with a further tablet that is unlikely to have any beneficial effect); and that the mechanism of benefit is unlikely to relate to the immediate consequence of altering the physio-chemical properties of cell membranes in the direction of electrical stability (which should have resulted in a much more rapid reduction in arrhythmia and by extension, sudden death).

CONCLUSIONS Polyunsaturated fatty acids have important theoretical benefits on the heart failure syndrome. There is mounting evidence of their benefit following acute myocardial infarction or in ischemic syndromes. The GISSI-HF study was designed to explore their effects in a population with stable chronic heart failure. The study has demonstrated that these agents can be administered safely to an elderly population of patients with heart failure. Fears about increasing infection susceptibility and inducing ventricular dysrhythmias have not been realized. The study also confirms the malignant nature of chronic heart failure, with a 30% mortality at 4 years despite optimal medical therapy and close follow-up by sub-specialist physicians. However, the size of any benefit is very small. We remain unconvinced of the benefit of ω-3 PUFAs in stable CHF patients on otherwise optimal medical therapy and do not believe they should be routinely prescribed.

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