The Clinical Benefit of Omega-3 PUFA Ethyl Esters Supplementation in Patients with Heart Failure

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ABSTRACT

Chronic heart failure, a syndrome of cardiac dysfunction associated with breathlessness, effort intolerance and fluid retention, affects 1-2% of the population. The most frequent cause is impairment of systolic function of the left ventricle, usually due to coronary artery disease. Hypertension or diabetes often co-exist. Treatment of heart failure (HF) is centred on correction of any reversible pathology and antagonism of the intense neurohormonal activation triggered by the cardiac dysfunction. This is achieved by angiotensin converting enzyme inhibitors (or angiotensin receptor blockers), beta-blockers and in more severe cases, an aldosterone antagonist. The prognosis of HF remains poor – with a first year mortality of over 30%, reducing to 10% per annum thereafter. Death is usually due to either progressive pump failure or sudden death, which is presumably arrhythmic in origin. A randomised double-blind controlled trial of 1g daily of omega-3 polyunsaturated fatty acids (PUFA) ethyl esters in almost 7000 patients with symptomatic chronic heart failure of any cause reported a 9% relative risk reduction in mortality (P=0.04) and 8% relative risk reduction in mortality or cardiovascular hospitalisation (P=0.009)(GISSI-HF). In absolute terms, 56 patients need to be treated for 3.9 years to prevent one death. International guidelines recommend the prescription of 1g daily of n-3 PUFA as an adjuvant to secondary prevention in patients after myocardial infarction (based on the results of GISSI-Prevenzione, published in 1999) and for those with hypertriglyceridaemia, but are likely to be updated to recommend this therapy for patients with heart failure also.

The clinical problem

Heart failure is a clinical syndrome of breathlessness, effort intolerance and fluid retention due to underlying cardiac dysfunction. The typical age of first diagnosis in developed countries is in the mid-70s, with the incidence being higher in men than in women at all age groups.(1) Recent estimates suggest that 1-2% of the population have heart failure, with a life-time risk of at least 1 in 5.(2) In developed countries, the single most common cause is coronary artery disease, often co-existent with hypertension and diabetes.(3)

The syndrome has a large impact on life expectancy and quality of life. Epidemiological studies suggest that the prognosis has improved considerably in the past two decades, most likely due to the introduction of drug therapies such as angiotensin converting enzyme inhibitors and beta-blockers. (4) Despite this, the mortality in the first year after diagnosis is around 30%, falling to 10% per annum thereafter if best therapy is used. Most deaths are due to either progressive heart failure or sudden arrhythmia – with patients with milder symptoms more likely to die suddenly and those with severe symptoms more likely to die of progressive pump failure.(6) Heart failure affects physical and emotional quality of life more than most chronic conditions,(7) and many patients remain symptomatic despite best therapy. Episodic deterioration can occur, particularly where chronic disease monitoring is poor or with intercurrent illness or arrhythmia. Duration of hospitalisation is typically around 10 days in Europe, with a high re-admission rate.(8) The cost of such hospitalisation drives the overall cost of heart failure care to the health service – with most countries reporting that 1-2% of their healthcare budget is spent on heart failure. (9) Recent data suggest that the hospitalisation rate is falling.(10) although the total number of people with heart failure rises steadily due to ageing of the population and the improved prognosis of the condition.
In Europe, the majority of cases of heart failure are due to obvious systolic dysfunction of the left ventricle (‘systolic heart failure’), most usually described by the reduction in ejection fraction (EF) to below 50%. Valve disease accounts for perhaps 10% of new cases, and 10-20% of cases are due to abnormalities of relaxation of the left ventricle (‘diastolic heart failure’, or ‘heart failure with normal ejection fraction’). This underlying abnormality is more common in the elderly, those with hypertension and/or diabetes, and appears to be more common in North America than in Europe.

**Guidelines for therapy**

There are high quality evidence-based guidelines available in North America (12) and Europe (13) with many countries also producing local guidelines, including the National Institute for Clinical Excellence (NICE) in England (14).

Heart failure, whatever the cause, is associated with fluid retention, intense vasoconstriction and neurohormonal activation – particularly of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Such responses to cardiac dysfunction help maintain vital organ perfusion in the short-term but are ultimately counter-productive and can lead to a downward spiral of cardiac and renal dysfunction. Arrhythmia is common in this setting, with atrial fibrillation in up to 40% of patients, and life-threatening ventricular arrhythmia causing death in 20-50% of patients.

Most of the evidence for drug therapy (and electrical devices such as cardiac resynchronisation and/or implantable cardioverter defibrillators) relates to systolic heart failure, with numerous large randomised controlled trials, well summarised in international guidelines (12,13).

**Figure 1** gives the key components of therapy for chronic heart failure due to systolic dysfunction of the left ventricle in the current ESC guideline for heart failure. (13)

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**Figure 1**: The treatment algorithm for patients with symptomatic heart failure and reduced ejection fraction. (Used with permission from Reference 13).
Evidence for benefit of supplementation of omega-3 PUFA ethyl esters in patients with cardiac disease

Animal and cellular work have suggested that omega-3 PUFA ethyl esters can decrease the propensity to arrhythmia, reduce inflammation, modulate autonomic and vascular tone, decrease platelet activation and affect ventricular response to hypertrophic stimuli. (15)

One of the landmark clinical studies of omega-3 PUFA ethyl esters supplementation in a high risk population was the GISSI-Prevenzione Trial, published in 1999. (16) More than 11,000 patients with a myocardial infarction (MI) within the past three months were randomised to 1g omega-3 PUFA ethyl esters daily, 300mg Vitamin E daily, both or neither, in addition to standard therapy for 3.5 years. Just over 40% of patients were treated with an ACE inhibitor and beta-blocker at baseline. The primary combined endpoint was mortality and non-fatal MI and stroke. Vitamin E had no effect, but omega-3 PUFA ethyl esters were associated with a 20% reduction in mortality, and a 45% reduction in the risk of sudden death. This effect was apparent within three months of therapy. Overall, the patients were only mildly symptomatic and had relatively well preserved systolic function of the left ventricle.

Subsequent analysis of the results of GISSI-Prevenzione reported that those patients with an EF < 50% had a higher risk of death (including sudden death) than those with better preserved ventricular function, as expected, but the relative risk reduction for total mortality with omega-3 PUFA ethyl esters was similar across all EF groups. (17) However, the benefit of omega-3 PUFA ethyl esters on sudden death was much greater in those with low EF – with a 4-fold greater relative risk reduction in those with an EF < 40% compared to those with an EF > 50%. (Figure 2).

GISSI-HF (18) set out to robustly test whether a daily dose of 1g of omega-3 PUFA ethyl esters would have a beneficial effect on patients with chronic heart failure, compared with placebo, in addition to best therapy with renin-angiotensin-aldosterone antagonists and beta-blockers. Data from 3494 patients randomised to omega-3 PUFA ethyl esters and 3481 randomised to placebo were compared over a median follow-up of 3.9 years. The trial also examined the effect of rosuvastatin 10mg compared with placebo, but found no evidence of benefit with this therapy.

Figure 2: Relative risk reduction for sudden cardiac death in the GISSI-Prevenzione trial, by ejection fraction category. (Modified with permission from reference 17)
The characteristics of the patients enrolled in GISSI-HF were not dissimilar to typical well-treated patients seen in outpatient clinics across Europe. Over 40% of patients were over the age of 70. Very few (<3%) patients were symptomatic at rest (NYHA Class IV), but a third were symptomatic on mild exertion (NYHA Class III), with almost two thirds being only symptomatic on moderate exertion (NYAH Class II). The vast majority had obvious systolic impairment of the left ventricle, with less than 10% having an EF > 40%. Around half of patients had ischaemic heart disease. 28% were diabetic and more than 50% had a history of hypertension. ‘Standard’ drug therapy was excellent, with 93% being on either an ACE inhibitor or ARB at baseline, 65% were on a beta-blocker and almost 40% were on the aldosterone antagonist, spironolactone. Only 7% had an implantable cardioverter defibrillator at the time of randomisation, and 20% were taking amiodarone.

The primary endpoint of the study was total mortality, with a secondary endpoint of total mortality and cardiovascular hospitalisation.

The added benefit of 1g omega-3 PUFA ethyl esters for this very well-treated group of heart failure patients was a 9% relative risk reduction in all-cause mortality [HR 0.91, 95% CI 0.83–0.99; P=0.04] with an absolute benefit of 1.8% (95% CI 0.3-3.9%) and number needed to treat of 56 patients for 3.9 years to prevent one death. Adding in cardiovascular hospitalisation, the relative risk reduction was very similar at 8% [HR 0.92, 95% CI 0.84–0.99; P=0.009], but with absolute benefit of 2.3% (95% CI 0.0-4.6%) with number needed to treat of 44 patients for median of 3.9 years to prevent either one death or one cardiovascular hospitalisation. Examination of the survival curves (Figure 3) suggests that the effect increased with time, becoming appreciable after 24 months of treatment. Formal cost-effectiveness analysis is underway and is likely to show that this clinical effect is achievable at a cost currently considered good value for money by bodies such as NICE.

Interestingly, the effect of omega-3 PUFA ethyl esters appeared to be very similar for both deaths due to progressive pump failure and presumed arrhythmic death: 9.1% dying of pump failure in the omega-3 PUFA ethyl esters group vs 9.5% in the control group, and 7.8% dying suddenly in the omega-3 PUFA ethyl esters group vs 8.7% dying suddenly in the control group. Prespecified subgroup analysis found no evidence that the beneficial effect of omega-3 PUFA ethyl esters differed by age, aetiology of heart failure, symptom severity or degree of left ventricular impairment. Prespecified per protocol analysis of those who had been compliant with the study medication for at least 80% of the time reported a 14% relative risk reduction in mortality [HR 0.86; 95% CI 0.77–0.95; P=0.004].

Omega-3 PUFA ethyl esters supplementation is known to be well tolerated, and the proportion of patients who had stopped taking the study medication in this study was similar in both the active and placebo groups (29% at end of the study), with permanent discontinuation due to side-effects, 3% in both groups, virtually always because of gastrointestinal symptoms.

The authors of the study commented that although the effect size was less than anticipated, it appeared to be consistent across all subgroups in the study. They argued, from basic and observational data, that omega-3 PUFA ethyl esters could have its beneficial effects not only by improving the arrhythmic milieu but also by modifying the ventricular and vascular response to neurohormonal activation triggered by the heart failure.

Omega-3 PUFA ethyl esters supplementation in international guidelines

Currently, omega-3 PUFA ethyl esters (for example, as a supplement containing 90% concentrate of eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) marketed as Omacor® in Europe) is licensed for treatment of increased blood triglycerides or hypertri-glyceridaemia and as adjuvant treatment in secondary prevention after myocardial infarction.

These clinical indications are supported in international guidelines. The European Society of Cardiology Guideline on management of ST elevation MI (published in 2008) recommends the consideration of prescription of 1g daily of omega-3 PUFA ethyl esters for patients with low intake of oily fish, and for those who cannot tolerate a statin.
The most recent guidance from the American Heart Association and other bodies is similar, stating that it may be reasonable to encourage increased omega-3 PUFA ethyl esters consumption in the form of fish or capsules (1g per day) [20]. Post-MI prevention guidelines from NICE (which also consider cost-effectiveness before making recommendations) suggest that such supplementation should be considered for up to four years after MI if a patient is not taking 2-4 portions of oily fish per week [21].

Although not yet licensed for use in patients with chronic heart failure, it is likely that updates on international guidelines will make a recommendation to at least consider increasing omega-3 PUFA ethyl esters consumption in the form of oily fish or capsules (1g per day) in patients with chronic heart failure already optimally medically treated. This recommendation would be based on consensus opinion on interpretation of one specific large randomised controlled trial in a heart failure population (GISSI-HF) [19] bolstered by supportive evidence from post-MI patients in GISSI-P [16] and other smaller randomised and observational studies.

**CONCLUSIONS AND RECOMMENDATIONS**

Heart failure is an important healthcare issue – with 1-2% of the population living with this chronic condition. Coronary artery disease remains the main driver for new cases. The evidence base is strongest for patients with underlying systolic dysfunction of the left ventricle. Drug therapy to improve prognosis and symptoms in this patient group should include ACE inhibitors (or ARBs), beta-blockers and often aldosterone antagonists. There is direct evidence from one large randomised controlled trial in heart failure (GISSI-HF), supported by indirect evidence from other randomised trials in patients with cardiac disease, that 1g daily supplementation of omega-3 PUFA ethyl esters can provide additional benefit in terms of saving lives and reducing the risk of hospitalisation. Such therapy is very well tolerated.

It is likely that adjuvant therapy with 1g omega-3 PUFA ethyl esters daily will be recommended for consideration by physicians and patients in heart failure guidelines in the near future. Currently such therapy is licensed as adjuvant therapy for secondary prevention after MI, and for the treatment of hypertriglyceridaemia.

**REFERENCES**