

New facts on the cardioprotective role of Omega-3 polyunsaturated fatty acids

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ABSTRACT

There is already important evidence regarding the beneficial effects of omega 3-polyunsaturated fatty acids (omega 3-PUFAs) on cardiac protection. Initial epidemiological observations on people who consumed large quantities of fish revealed higher life-expectancy and fewer cardiovascular events in comparison with subjects who consumed less fish. This possible link between fish consumption and cardiac events led to further prospective trials, in order to better understand their mechanism of action and protective role. There is now strong evidence of an early and large reduction in the risk of sudden cardiac death with omega-3 PUFAs in post-myocardial infarction patients, probably related to their anti-arrhythmic effect. Meanwhile, there are several studies suggesting a decrease in the onset of atrial fibrillation after cardiac surgery, associated with fewer complications and a better outcome. Furthermore, acting upon different mechanisms for the development of heart failure, there are new encouraging reasons to believe that omega 3-PUFAs might delay its progression, and play an important role in heart failure prognosis. This article is a review of the latest data summarizing the current knowledge on the role of omega 3-PUFAs for cardiac protection.

Keywords: omega-3 polyunsaturated fatty acids, arrhythmias, myocardial infarction, heart failure

1. INTRODUCTION

More than 30 years ago a possible relationship between fish consumption and cardiac mortality started to raise an interesting hypothesis. At that time, observational data showed a 50% higher life-expectancy in Greenland Inuits who consumed at least 30 g of fish daily, by comparison with similar populations eating no fish (1,2). The key ingredient in this diet influenced by this traditional way of living is a large amount of polyunsaturated fatty acids

found in fish and fish oils. Since then, there has been an increase in both the scientific and the public interest concerning the role of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) in the management of cardiovascular diseases.

Recent controlled clinical trials investigated three major areas of interest regarding the cardioprotective role of omega-3 PUFAs:

1. prevention of life-threatening arrhythmias, resulting in the reduction of mortality in post-myocardial infarction (MI) patients;

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2. prevention of atrial fibrillation in post coronary artery by-pass surgery patients;
3. prevention of progression of heart failure. This review, based on a recent symposium held during the World Congress of Cardiology (WCC) in Barcelona, Spain, will discuss briefly these new developments regarding the cardioprotective role of omega-3 PUFAs.

2. EFFECTS OF OMEGA-3 PUFAS ON LIFE-THREATENING ARRHYTHMIAS

2.1. Low risk population

Several epidemiological studies successfully sustained an inverse correlation between the omega-3 PUFAs blood level and the risk of sudden cardiac death. And indeed, as compared with subjects whose blood levels of omega-3 PUFAs were in the lowest quartile, the relative risk of sudden death was significantly lower among subjects with levels in the third quartile (adjusted relative risk, 0.28; 95%CI, 0.09 to 0.87) and the fourth quartile (adjusted relative risk, 0.19; 95%CI, 0.05 to 0.71), suggesting that omega-3 PUFAs found in fish are strongly associated with a reduced risk of sudden death among subjects without evidence of prior cardiovascular disease (3).

Furthermore, He et al conducted a meta-analysis to examine the association between fish intake and coronary heart disease mortality. A database was developed on the basis of 11 eligible studies and 13 cohorts, including 222,364 individuals with an average 12 years of follow-up. Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish showed lower coronary heart disease mortality; the relative risks for coronary heart disease 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/day increase in fish intake was related to a 7% lower risk of coronary heart disease mortality (4).

These epidemiological data suggested a possible anti-arrhythmic effect of the omega-3 PUFAs, confirmed by further elegant experiments. A study conducted in a canine model enabled scientists to confirm the anti-arrhythmic

effects of omega-3 PUFAs. This model involves surgical ligation of the left anterior descending artery, which induces a non-fatal myocardial infarction, and the fitting of an inflatable cuff around the circumflex artery. By inflating the cuff during exercise, an ischemia-induced ventricular fibrillation (VF) develops. Intravenous administration of omega-3 PUFAs was responsible for increasing the threshold of VF development, and also for reducing the arrhythmia-induced mortality by 25%-30%. When given soya bean oil, the results were not reproducible. It should be emphasized that experimental mechanisms may be different when compared with real *in vivo* clinical studies, offering a possible explanation for the somehow discordant clinical results (5).

2.2. High-risk population (post-myocardial infarction)

Several clinical prospective studies followed the epidemiological retrospective ones and animal experiments, in an attempt to demonstrate the same beneficial effects of omega-3 PUFAs on coronary mortality.

The first such study was done on 2033 men with a previous myocardial infarction, randomized to a diet rich or not in fish oil (DART study). Both total mortality and coronary mortality were significantly decreased after 2 years follow-up (by 29% and 32%, respectively) in patients receiving omega-3 PUFAs rich diet (6).

The GISSI-Prevenzione trial was a 3.5-year open study in 11,323 patients who had experienced a myocardial infarction < 3 months before enrolment, randomized to receive highly purified omega-3 PUFAs (1 g/day), vitamin E (300 mg/day), both medication or neither, while using recommended and approved secondary preventive therapies (7,8). During the 3.5 years follow-up period, the use of highly purified omega-3 PUFAs was associated with a 15–20% reduction in the relative risk of experiencing a primary endpoint event (death, myocardial infarction or stroke). The most stunning result was the sustained benefit on the risk of sudden cardiac death, with a 44% reduction (figure 1). Moreover, there was clear evidence of treatment effect within the first 4 months of the study (figure 2). The anti-arrhythmic effects of highly purified omega-3 PUFAs in ischemic-induced conditions (such as post-myocardial infarction) were held “responsible” for the marked risk

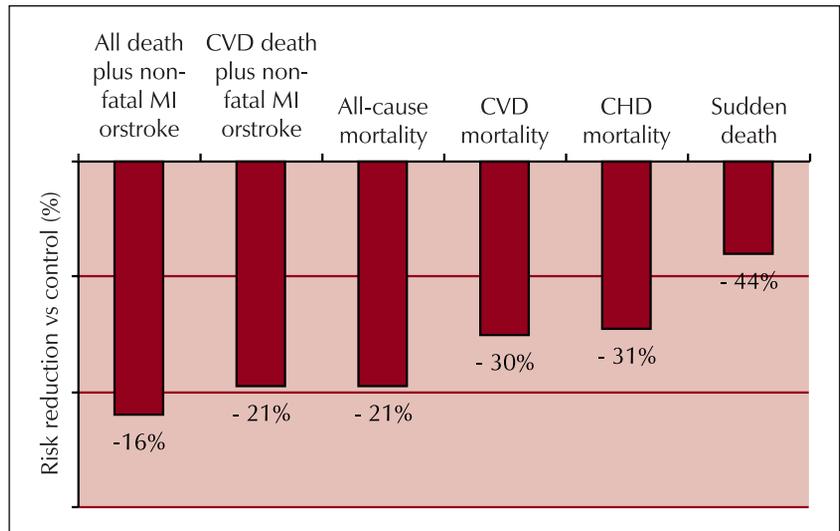


FIGURE 1. Risk reduction in GISSI-Prevenzione trial.

In GISSI-Prevenzione trial, the use of omega 3-PUFAs was associated with a 15-20% reduction in the relative risk of experiencing a primary endpoint event (death, myocardial infarction or stroke), the most stunning result being the 44% reduction in the risk of sudden cardiac death (modified from 8).

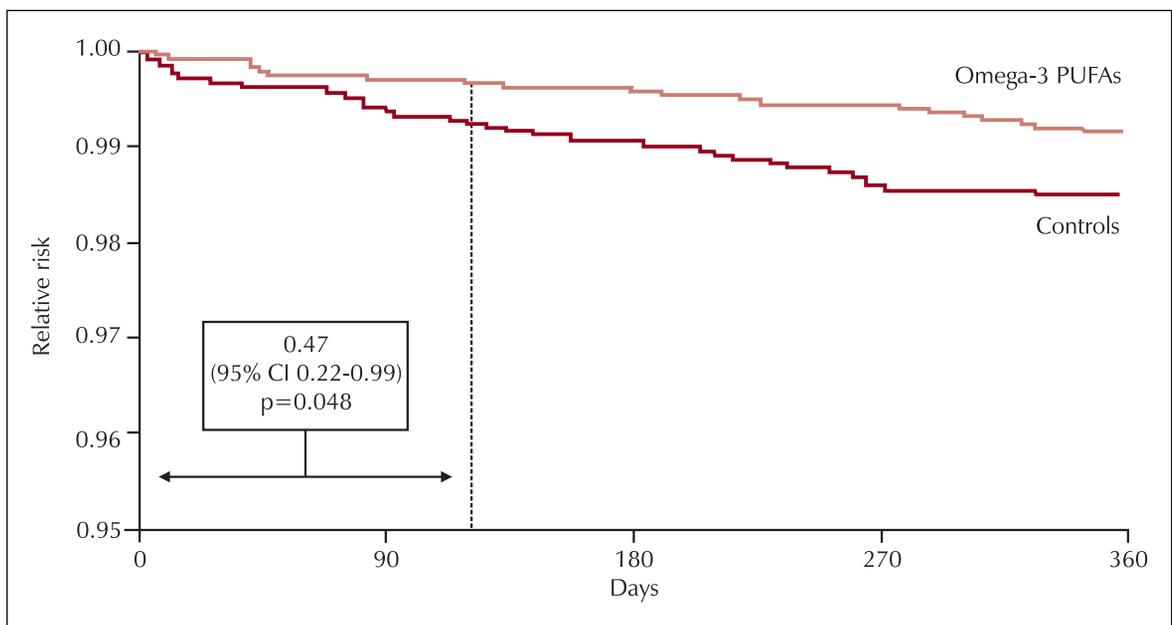


FIGURE 2. Early risk reduction of sudden death in the GISSI-Prevenzione trial.

Use of omega 3-PUFAs was associated with an early and large reduction in the risk of sudden cardiac death in GISSI-Prevenzione study (modified from 8).

reduction of sudden cardiac death in the GISSI-Prevenzione trial (9).

2.3. Studies on ICD populations

The surprisingly beneficial results of GISSI-Prevenzione trial were the starting point for several studies on patients with implantable cardioverter defibrillator (ICD). The continuous

monitoring by ICD allowed a suitable and reliable study of the possible anti-arrhythmic effects of omega-3 PUFAs in these patients. Three small-scale studies in such patients have been reported so far.

In the first of these, Raitt et al could not show an effect of omega-3 PUFAs supplementation (1.8 g/day) on the risk of ventricular tachycardia

(VT) and ventricular fibrillation (VF) in 200 patients treated for a median of 718 days (20-828 days) (10).

The second of these studies in ICD populations was the Fatty Acid Arrhythmia Trial (FAAT) (11). The trial initially enrolled 402 patients who were randomized to omega-3 supplementation or olive oil control, for a planned follow-up period of 12 months. But the high rate of non-compliance (35%) in both groups, and full follow-up data obtained only for 109 participants did not guarantee sure and reliable results. Those results were in fact supportive of a benefit from omega-3 PUFAs therapy. There was a relative risk reduction of 28% in the intention-to-treat analysis for the endpoint of first confirmed ICD shock for VT or VF, or death from any cause among patients assigned to omega-3 PUFAs therapy ($p = 0.057$). The relative risk reduction became significant (31%; $p = 0.033$) when probable episodes of VT or VF were included. Among patients who remained on protocol-specified therapy for at least 11 months there was evidence of benefit from omega-3 therapy, with

a relative risk reduction of 38% ($p = 0.034$) (figure 3). Omega-3 PUFAs therapy was also associated with a borderline significant reduction in the total number of ICD shocks delivered ($p = 0.07$).

About at the same time, another trial (Study on Omega-3 Fatty Acids and Ventricular Arrhythmia, SOFA) investigated effects of omega-3 PUFAs on ICD patients (12). 546 patients with an average age of just over 60 years were randomized to placebo or on omega-3 PUFAs supplement (2 g/day) for a median period of 1 year. Overall, the study showed no significant benefit from supplemental fish oil.

The controversial results of the ICD trials failed to fulfill the high expectations to confirm the anti-arrhythmic effect of omega-3 PUFAs, as anticipated after the publication of the GISSI-Prevenzione data. However, the different mechanisms responsible for the development of life-threatening arrhythmias may be incriminated in the lack of consistency of results reported in these studies. Thus, in the GISSI-Prevenzione trial the arrhythmias were ischemia-induced (<3 months post-MI patients), whereas in the ICDs patients, most cases of arrhythmia occurred as a direct result of the re-entry circuits inside severe affected scarred ventricles (12). Therefore, further adequately powered clinical trials should be developed to corroborate the findings of GISSI-Prevenzione and to identify more accurately the types of patients who can be expected to benefit most from omega-3 PUFAs therapy.

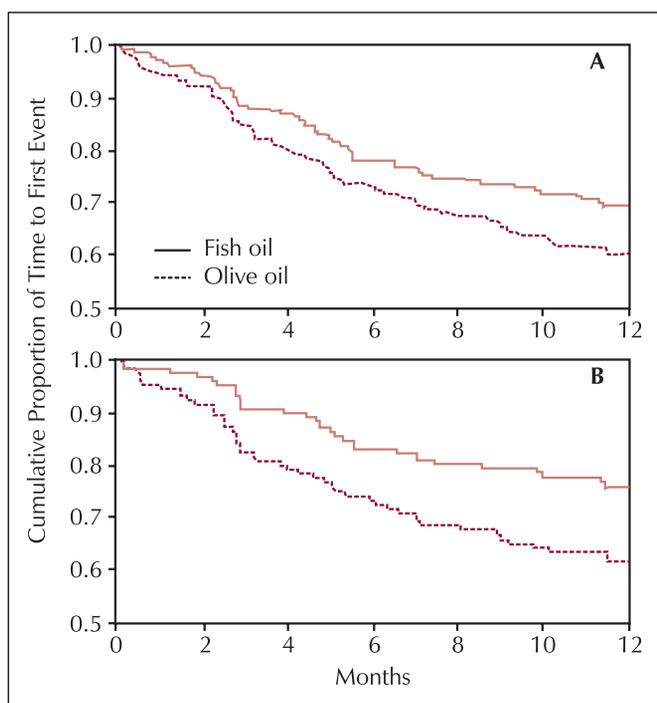


FIGURE 3. Kaplan-Meier analyses of the time to ICD shock for VT/VF or death

Curves in graph A are based on the intent to treat analysis; there was a risk reduction of 28% ($p = 0.057$) for the endpoint of first confirmed ICD shock for VT or VF or death from any cause, among patients assigned to omega-3 PUFAs therapy. Curves in graph B are limited to only those compliant for at least 11 month (risk reduction of 38%; $p = 0.034$) (modified from 23).

3. EFFECTS OF OMEGA-3 PUFAS ON ATRIAL FIBRILLATION IN POST CORONARY ARTERY BY-PASS SURGERY PATIENTS

Atrial fibrillation (AF) is the cardiac arrhythmia most often encountered in cardiology practice. The coronary artery by-pass grafting (CABG) increases the risk of developing atrial fibrillation; 30% of patients undergoing CABG-only surgery experience AF, and even a larger percent, =50%, when CABG is accompanied by valve surgery (13, 14).

The acute and most frequently high heart rate AF in post CABG patients might have serious adverse events, such as loss of atrial pump, low cardiac output (in relation with cardiac function prior to AF onset), heart failure, and embolic stroke. Prevention of post-CABG atrial fibrillation is therefore required, enabling favorable evolution of these patients.

Initial epidemiological studies suggested that fish oil might decrease the risk of AF in an elderly population, but the results were rather controversial. Thus, in a prospective, epidemiological cohort of 4815 adults, followed up to 12 years, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% lower risk with intake 1 to 4 times per week, and 31% lower risk with intake =5 times per week, compared with <1 time per month (15). However, on the contrary, a similar study on 5184 subjects did not support a significant relation (16).

Looking upon the effects on post-CABG atrial fibrillation, Calo et al reported promising results in 160 patients randomized prospectively to a control group or omega-3 PUFAs 2 g/day, for at least 5 days before elective CABG and until the day of discharge from the hospital. Postoperative AF developed in 33% of the control group and in 15% of the omega-3 PUFAs group (54% reduction, $p = 0.013$). Moreover, after CABG, the omega-3 PUFAs patients were hospitalized for significantly fewer days than controls (7.3 ± 2.1 days vs. 8.2 ± 2.6 days, $p = 0.017$). This study demonstrated for the first time that omega-3 PUFAs administration during hospitalization in patients undergoing CABG, substantially reduced the incidence of postoperative AF and was associated with a shorter hospital admission period (17).

Recently, a new clinical trial (PROFI) has been initiated by Australian scientists, as Professor Kostner communicated during the WCC meeting in Barcelona. This on-going trial is placebo-controlled and will enroll 200 patients, aged =65 years, with no history of previous chronic atrial fibrillation or flutter. These patients will receive either 1 g/day of omega-3 PUFAs or placebo for 1–4 weeks before elective CABG surgery. The primary endpoint of the study is incidence of AF within 30 days after CABG.

Mechanisms by which omega-3 PUFAs may reduce the risk of AF include alterations in membrane fluidity, with resultant effects on the action of transmembrane ion channels and increased resistance to stretch-induced AF. Reduced synthesis/release of pro-inflammatory mediators has also been proposed (18).

Nevertheless, prevention of the onset of AF after undergoing CABG surgery is not the sole purpose when studying omega-3 PUFAs administration. Control of the heart rate by slowing the atrio-ventricular conduction may be another effect associated with increased dietary omega-3 PUFAs intake. Thus, successful rate

control by omega-3 PUFAs might reduce the need for anti-arrhythmic drugs, and so reduce the potential for the adverse effects of such drugs.

4. POTENTIAL BENEFITS OF OMEGA-3 PUFAS IN HEART FAILURE PATIENTS

Heart failure (HF) is still a deadly syndrome. Mortality from heart failure worldwide is similar with mortality from myocardial infarction, and higher than mortality from cancer (19). Meanwhile, prevalence of heart failure is increasing continuously, both in men and in women, as shown by a recent epidemiological study comparing the prevalence in the 70's with the prevalence after 20 years, in the 90's (20). This is an intriguing subject, since modern medicine provides us with a wide range of therapeutic choices. This apparent paradox could be explained by the under-use of beneficial medications, as suggested by the EuroHeart Failure Survey, where ACE-inhibitors were used only in 62% of the patients, beta-blockers in 36%, and spironolactone in less than 25% (21). The majority of new therapies, such as new vasodilators (natriuretic peptides or vasopeptidase inhibitors) or new positive inotropic agents (PDE inhibitors or calcium sensitizers), proved to have no effect or even increase mortality in patients with heart failure.

Patients with heart failure can die acutely from sudden cardiac death or pulmonary embolism, or die "chronically" from the progression of heart failure (figure 4). By acting

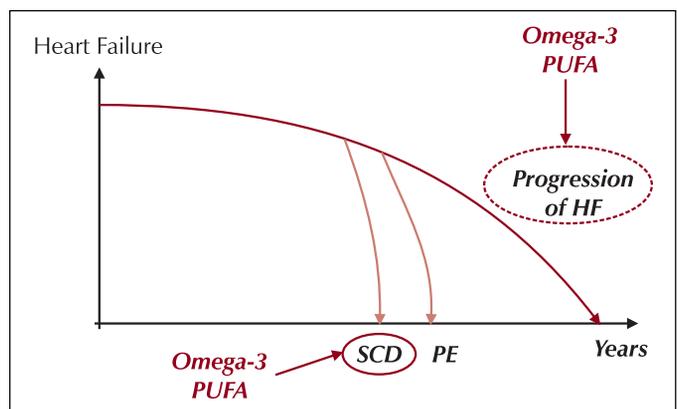


FIGURE 4. Effects of omega-3 PUFAs on the natural history of heart failure

Patients with heart failure can die brutally from sudden cardiac death or pulmonary embolism, or die "chronically" from the progression of heart failure. Omega-3 PUFAs can act on sudden cardiac death (22), and also on the progression of heart failure (31).

on each of these mechanisms, omega-3 PUFAs might have a positive impact on heart failure mortality and morbidity.

4.1. Effects on sudden cardiac death in patients with heart failure

The most powerful evidence to support the effect of omega-3 PUFAs on sudden cardiac death in patients with heart failure results from a sub-analysis of the GISSI-Prevenzione trial (22). A clear-cut reduction in sudden death was seen with omega-3 PUFAs therapy in the overall GISSI-Prevenzione trial, with a relative risk of 0.55 (95% CI, 0.40–0.76) compared with controls. Further analysis of data revealed that the effect of omega-3 PUFAs on risk of sudden death was inversely related to baseline left ventricular ejection fraction (figure 5).

4.2. Effects on progression of heart failure

The progression to heart failure is a result of many pathological and physiological interactions. Thus, a myocardial injury, caused by e.g. hypertension or diabetes, induces neurohormonal activation which promotes myocardial fibrosis. Concomitant, it induces endothelial dysfunction with increased arterial stiffness, which promotes myocardial ischaemia. Myocardial fibrosis and ischaemia are inter-

related, since ischaemia is the most important determinant of fibrosis, and perivascular fibrosis aggravates ischaemia. Fibrosis and ischaemia are the main mechanisms of early left ventricular dysfunction, which activates the compensatory mechanisms of hypertrophy and dilation. When these are surpassed, progressive heart failure develops.

Omega-3 PUFAs have been shown in experimental studies and small-scale clinical investigations to have favorable effects on several of these aspects of the heart failure pathology. For example, endothelium-dependent forearm blood flow is enhanced by omega-3 PUFAs (24,25) and arterial stiffness is reduced (26). This mechanism might be important, since we proved that arterial stiffness, by promoting subendocardial ischaemia, is inversely related to the left ventricular systolic and diastolic function (27). Therefore, by decreasing arterial stiffness, we would expect omega-3 PUFAs to decrease myocardial ischaemia. And indeed, in an experimental study in rats, it was shown that a diet rich in omega-3 PUFAs improved heart metabolism during ischaemia, by increasing efficiency of cardiac oxygen use at any level of the filling pressure, also at high pressures as present in patients with heart failure, by comparison with a normal diet or a diet rich in saturated animal fat (28). By reducing the negative effects of myocardial ischaemia, omega-3 PUFAs might prevent ventricular hypertrophy and dilatation, as suggested recently in an experimental model of cardiomyopathy (29). Moreover, other studies have suggested that omega-3 PUFAs might exert anti-fibrotic cardiac effects (30).

Epidemiological data are supportive of the results of these mechanistic studies. A recent epidemiological trial on 4738 subjects followed for 12 years, demonstrated that progression to heart failure is decreased significantly by a diet rich in omega-3 PUFAs, showing a negative correlation between the omega-3 PUFAs intake and the relative risk of progression to heart failure (31).

Thus, there is a range of data to suggest that omega-3 PUFAs may prevent the progression of HF. This hypothesis is now being tested in the GISSI Heart Failure Study (GISSI-HF). This is a large, prospective, multicenter trial designed to examine the effects of omega-3 PUFAs 1 g/day versus placebo on mortality and morbidity

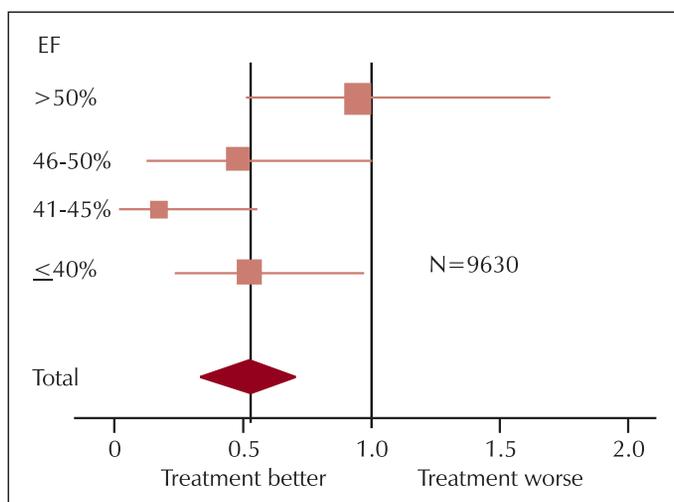


FIGURE 5. Reduction in risk of sudden death and the ejection fraction

A subgroup analysis of outcomes data on a large subset of patients enrolled in GISSI-Prevenzione revealed that the scale of the reduction in the risk of sudden death was inversely related to baseline left ventricular ejection fraction (modified from 22). Similar results were reported in the FAAT study for patients who were compliant with the study regimen of omega-3 PUFAs supplementation for more than 11 months (23).

in approximately 7000 patients with mild to severe CHF (New York Heart Association classes II–IV), and ejection fraction <40% or at least one hospitalization for HF (figure 6). The results of this study will provide answers to the question of whether or not omega-3 PUFAs are beneficial in chronic heart failure. A second randomization in GISSI-HF will examine the potential benefit of aggressive lipid-lowering therapy with rosuvastatin in patients with CHF. It is expected that GISSI-HF will be completed towards the end of 2007 (32).

5. Conclusion

Cardiovascular diseases are still the leading cause of mortality and morbidity worldwide. The pathological mechanisms are not entirely understood and the therapeutic regimes are open to further debate. Experimental and clinical data on omega-3 PUFAs are promising, showing that: 1. there are important evidences of mortality reduction in post-myocardial infarction patients with low-dose of highly purified omega-3 PUFAs; 2. there is a possible indication for omega-3 PUFAs in preventing postoperative atrial fibrillation, in patients undergoing coronary artery by-pass; and 3. there is a potential benefit of omega-3 PUFAs in heart failure, which is now being examined in a major clinical outcome trial.

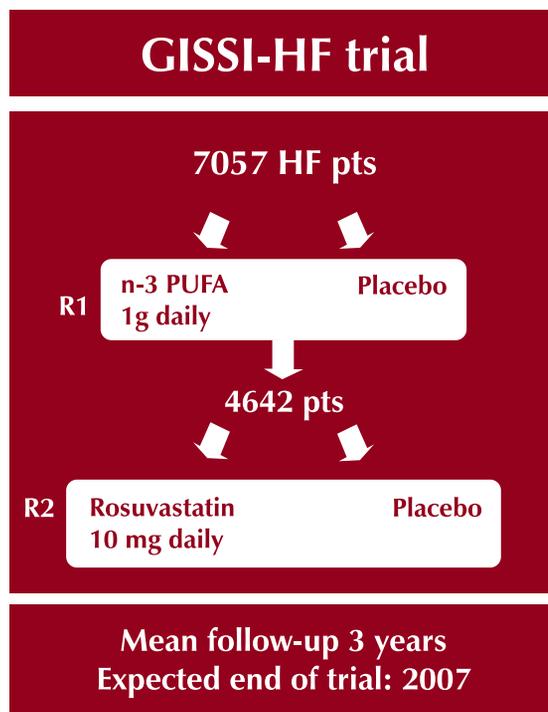


FIGURE 6. GISSI-Heart Failure trial design
 This is an on-going study, on mild to severe CHF, meant to assess the effects of omega-3 PUFAs therapy on mortality and morbidity, and the possible benefits from aggressive lipid-lowering therapy with rosuvastatin (32).

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