N-3 Polyunsaturated Fatty Acids Reduce Heart Failure–Related Admissions and Death

GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223–30.

Study Overview

Objective. To investigate whether n-3 polyunsaturated fatty acids (PUFAs) can improve morbidity and mortality in patients with symptomatic heart failure.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. Industry-supported trial involving 326 cardiology and 31 internal medicine centers in Italy. The trial enrolled men and women aged ≥ 18 years with clinical evidence of heart failure due to any cause (classified as New York Heart Association class II–IV) and with a left ventricular ejection fraction (LVEF) measured within the prior 3 months. When LVEF was > 40%, patients were required to have been admitted to a hospital for heart failure within the past year. Exclusion criteria included known contraindication to, hypersensitivity to, or indication for n-3 PUFA; noncardiac comorbidity unlikely to be compatible with sufficient follow-up; acute coronary syndrome or revascularization within 3 months of enrollment; planned cardiac surgery; current investigational drug treatment; significant liver disease; and pregnancy or lactation. Study participants continued their baseline treatment for heart failure with a variety of cardiac medications.

Main outcome measures. Time to death and time to death or hospital admission for cardiovascular reasons. Secondary outcomes were cardiovascular mortality with or without admission, sudden cardiac death, and hospital admission for cardiovascular reasons, myocardial infarction, stroke, or heart failure.

Main results. Nearly 80% of study participants were men, and the mean age was 67 years. About 50% of the study participants had been hospitalized for heart failure symptoms during the year prior to enrollment. 7046 eligible patients were randomized to n-3 PUFA (1 g/day) or placebo. The median follow-up was 3.9 years. Of 3529 patients in the n-3 PUFA group, 37 were disqualified or lost to follow-up, while 40 of the 3517 patients in the placebo group were disqualified or lost to follow-up. The remaining patients were analyzed on an intent-to-treat basis. 955 (27%) patients died in the n-3 PUFA group as compared with 1014 (29%) in the placebo group (adjusted hazard ratio [HR], 0.91 [95.5% confidence interval {CI}, 0.833–0.998]; $P = 0.041$). 1981 (57%) patients in the n-3 PUFA group died or were admitted to the hospital for cardiovascular reasons, as compared with 2053 (59%) patients in the placebo group (adjusted HR, 0.92 [99% CI, 0.849–0.999]; $P = 0.009$). The absolute risk reduction was 1.8% (95% CI, 0.3–3.9) for all-cause mortality and 2.3% (95% CI, 0.0–4.6) for the combined endpoint. Death due to cardiovascular cause, overall hospital admissions, and hospital admissions due to cardiovascular causes were also significantly lower in the n-3 PUFA group. The majority of deaths in both groups were due to worsening heart failure. Although triglycerides were mildly lowered in the n-3 PUFA group, blood pressure and heart rate were unchanged. A similar number of patients in each arm discontinued the study drug (29% vs. 30%). The rate of discontinuation due to side effects was 3% in both groups, with gastrointestinal disturbance the most commonly reported side effect.

Conclusion. Use of n-3 PUFA reduced all-cause mortality and hospital admissions due to heart failure. Adverse effects were minimal and similar between the n-3 PUFA and placebo groups.

Commentary

Strong public interest exists regarding the use of fish oil to prevent or treat a variety of ailments, especially cardiovascular disease [1]. A recent U.S. study reported that 2% of the general population, 1% of patients with diabetes, and 0.5% of patients with cardiovascular disease use fish oil regularly [2]. N-3 PUFA, the putative active ingredient in fish oil, has been the focus of a flurry of research over the past decade. Recent studies suggest a conflicting pattern of evidence regarding the role of n-3 PUFAs (also known as omega-3 PUFA) in reducing or delaying cardiovascular disease. The GISSI-Prevenzione trial was an early milestone study that evaluated the effect of omega-3 PUFA supplementation in patients who had survived a myocardial infarction within the past 3 months [3]. The trial showed a small but statistically significant reduction in the risk of a composite cardiovascular event endpoint among patients who received omega-3 PUFA [3]. In subgroup analyses, a large proportion of the decrease in the composite endpoint was due to a reduction in sudden cardiac deaths, although the study was not designed to evaluate this specific outcome [4]. Subsequent laboratory studies have suggested that n-3 PUFA reduces electrical excitability as well as fatal and nonfatal arrhythmias in in vitro and in vivo models [5]. However, 3 small randomized clinical trials evaluating the antiarrhythmic effects of omega-3 PUFA have shown conflicting results. Notably, study patients had implantable defibrillators and thus likely had different reasons for sustained arrhythmias (eg, myocardial scar) than the postinfarction patients in the GISSI-Prevenzione study (eg, recurrent ischemic event) [4]. A subsequent meta-analysis of the 3 trials did not demonstrate a benefit of omega-3 PUFA supplementation in preventing ventricular arrhythmia [1]. A recent systematic review found omega-3 PUFA had no statistically clear beneficial effect on total mortality, cancer, or combined cardiovascular events [6].

The purpose of the study by the GISSI-HF investigators was to test whether supplementation with n-3 PUFA reduced morbidity and mortality among a large group of Italian patients with symptomatic heart failure. The study found that the number of deaths and admissions to the hospital for worsening heart failure was modestly but statistically significantly reduced in the intervention group. This study was a double-blind, controlled trial with excellent randomization. Its external validity is bolstered by the inclusion of a representative sample of nearly all cardiology centers in Italy. Few patients were lost to follow-up, and the sample sizes in each group gave the study adequate power to detect differences.

A few limitations deserve mention. The study showed a decrease in mortality and admissions in the treatment arm that was statistically significant. Although there was a concomitant decrease in sudden cardiac death, it was statistically insignificant. Thus, the investigators were unable to prove one of their main hypotheses: that n-3 PUFAs lower cardiac event rates due to stabilization of cardiac membranes and resultant decreases in arrhythmias. In addition, it is important to note that the trial was funded by industry sources, including the maker of fish oil supplements; however, it was stated that the funding companies had no role in the analysis or interpretation of the results. Finally, the study participants were primarily older white men. Inclusion of a greater number of women and nonwhite participants in future trials will be important to ensure generalizability across different populations.

Applications for Clinical Practice

Supplementation with n-3 PUFA appears to confer a modest mortality and morbidity benefit for older, primarily male patients with symptomatic heart failure already on standard medical treatment. n-3 PUFA supplements were well-tolerated with minimal side effects. However, because the results of other trials raise questions as to the overall efficacy of n-3 PUFA supplements on reducing cardiovascular disease, further research is needed to confirm these encouraging findings for heart failure patients.

—Review by Asaf Bitton, MD

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