Polyunsaturated Fatty Acids in Heart Failure
Should We Give More and Give Earlier?*

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There is an emerging paradox that confronts the care for patients with heart failure. On the one hand is the well-chronicled, woeful underutilization of evidence-based, guideline-supported therapies (1). On the other hand is the growing recognition that a monolithic approach to this very complex and heterogeneous disease is suboptimal. While we strive to fulfill performance measures, we simultaneously aspire to refine and individualize patient care and demand “evidence” to target new treatments to the subset of patients who will benefit most. It is with this background and with a decade-long drought in new drug therapies for heart failure that the story of n-3 polyunsaturated fatty acids (PUFAs) in heart failure prevention and treatment has unfolded. Over the last 3 decades, an extensive body of observational, experimental, and now randomized clinical trial data has built upon the initial observations of Bang and Dyeberg (2) to present a compelling storyline for the benefits of n-3 PUFAs in cardiovascular disease, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Animal and human studies have provided insights into the mechanisms by which these benefits may be achieved, including improvements in blood pressure and systemic vascular resistance, autonomic function, cardiac relaxation and filling, ventricular remodeling, arrhythmic risk, coagulation and thrombosis, and inflammation (Fig. 1) (3,4).

In 1999, the GISSI (Gruppo Italiano per lo Studio della Sopraovvivenza nell’Infarto Miocardico) Prevenzione trial represented the culmination of an extensive body of literature showing a 10% to 20% reduction in fatal and nonfatal cardiovascular end points in patients receiving moderate doses of n-3 PUFAs. The trial demonstrated a 21% relative risk reduction in death among patients taking 1 g of n-3 PUFAs (containing 850 to 882 mg of EPA/DHA ethyl esters with a ratio of 1:1.2) after myocardial infarction. This was achieved principally due to a reduction in sudden cardiac death (5). Post hoc subgroup analysis revealed that this reduction in sudden cardiac death was concentrated in patients with systolic dysfunction (relative risk: of 0.42 [95% confidence interval: 0.26 to 0.67]), and was in fact nonsignificant in patients with left ventricular ejection fraction >50% (6).

Beyond their use in the treatment of known cardiovascular disease, the last decade has seen a series of large epidemiological studies providing evidence for the effectiveness of n-3 PUFAs in preventing the development of heart failure. During 12 years of follow-up, the Cardiovascular Health Study demonstrated that among 4,738 elderly subjects, consumption of baked/broiled fish or supplemental n-3 PUFAs conferred a lower risk of incident heart failure (7). This risk was inversely proportional to the quantity of fish/supplement intake with a 32% relative risk reduction in patients consuming the equivalent of ≥1 g/day of n-3 PUFA, and the trend across consumption categories achieved statistical significance (7). In contrast, patients consuming much lower quantities of fish (the equivalent of 28 to 313 mg/day of n-3 PUFAs) in the Rotterdam study had no significant risk reduction (8). The large JACC (Japan Collaborative Cohort) study reaffirmed the inverse relationship between fish and supplemental n-3 PUFA intake and heart failure–associated mortality, although the trend only achieved statistical significance in patients taking supplemental n-3 PUFA (9). These results were further corroborated by data from the ARIC (Atherosclerosis Risk in Community) study, which demonstrated that higher plasma levels of DHA were associated with a lower risk for developing heart failure in women (10).

Cumulatively, these findings contributed to the hypothesis that n-3 PUFA supplementation in relatively high doses would result in reductions in heart failure–associated morbidity and mortality in patients with established heart failure of any etiology, and that these effects would be largely driven by reductions in nonfatal arrhythmic complications and sudden cardiac death as in GISSI-Prevenzione. To investigate this hypothesis, the GISSI-HF trial enrolled nearly 7,000 patients with New York Heart Association (NYHA) functional class II to IV heart failure and randomized them to 1 g/day of n-3 PUFA versus placebo on top of optimal medical care. Over the 3.9-year median follow-up, n-3 PUFA use resulted in a modest 9% relative risk reduction in all-cause mortality and an 8% reduction in the composite of mortality and cardiovascular hospitalization (11). Surprisingly, these benefits were conferred without a reduction in sudden cardiac death, hospitalizations for heart failure, or

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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Arrhythmia. An echocardiographic substudy also found small but significant improvement in left ventricular ejection fraction with n-3 PUFA but not with rosuvastatin (12). Although providing the strongest evidence to date for the role for n-3 PUFA in established heart failure, GISSI-HF managed to generate as many questions as it answered. How were these benefits achieved? Why was the risk reduction so small compared with that anticipated by prior data? Which patients with heart failure benefit most? Was the n-3 PUFA dose insufficient? The desire to answer these questions and the lack of a second large confirmatory trial have clearly contributed to the ambivalence towards adopting n-3 PUFA use in the broader heart failure population and incorporating the recommendation into current guidelines.

In this issue of the Journal, Nodari et al. (13) report results from a mechanistic study of 133 subjects examining the effect of n-3 PUFA therapy on conventional measures of systolic and diastolic dysfunction, ventricular remodeling, and functional impairment. Although not a prespecified end point with relatively small event rates, the marked reduction in cardiovascular and heart failure hospitalizations in the current study stand in stark contrast to the modest reduction present in GISSI-HF. Although patients in both studies were generally on optimal medical therapy, several contrasts between this study and GISSI-HF are illustrative. First, this study was confined to patients with angiographically proven nonischemic cardiomyopathy as compared with patients in GISSI-HF who may have had heart failure from any etiology. Furthermore, in contrast to GISSI-HF, this study focused on a patient population with less advanced heart failure, having a mean left ventricular ejection fraction of 37% (vs. 33% in GISSI-HF), NYHA functional class I to II symptoms (vs. approximately 40% of patients with NYHA functional class III or IV symptoms in GISSI-HF), and no deaths during the 12 months of follow-up. Pre-defined subgroup analysis from GISSI-HF suggested a stronger trend favoring n-3 PUFA use in patients with NYHA functional class II symptoms as compared with those with NYHA functional class III or IV symptoms (hazard ratio: 0.93, 95% confidence interval: 0.86 to 1.01) (11). Analogously in the current study, multivariate analysis demonstrated that a shorter duration of heart failure predicted subsequent improvements in left ventricular ejection fraction. Finally, one-half of the patients enrolled in GISSI-HF experienced a heart failure hospitalization within the previous year, alluding to their overall poorer prognosis (14).

Figure 1 Beneficial Effects of n-3 PUFAs in Heart Failure

AA = arachidonic acid; COX = cyclooxygenase; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ET = endothelin; ICAM = intracellular adhesion molecule; IL = interleukin; NF-KB = nuclear factor kappa B; NO = nitric oxide; PAF = platelet activating factor; PPAR = peroxisome proliferator-activated receptor gamma; SBP = systolic blood pressure; SVR = systemic vascular resistance; TNF = tumor necrosis factor; TxA2 = thromboxane A2; VCAM = vascular cell adhesion molecule; PUFA = polyunsaturated fatty acids.
contrasting results of these 2 trials suggest the possibility that n-3 PUFA s are most effective when introduced early in the course of cardiomyopathy, when they may potentially exert effects on viable myocardium. This type of divergent effect across the spectrum of heart failure has been proposed for other drugs such as statins (15), and should n-3 PUFA therapy be considered, they should be given prior to advanced stages of heart failure.

Another significant difference is the fact that subjects in the current study were given higher doses of n-3 PUFA s (~5 g of EHA/DPA daily for a month and ~2 g for the remainder of the study) than those given in GISSI-HF (~1 g of EHA/DPA). On the basis of the lack of any subject withdrawal and the high level of compliance as assessed by pill counting, this formulation of n-3 PUFA appears well tolerated. Answering the question of whether or not higher or “pulse” doses of n-3 PUFA s can achieve more favorable clinical and echocardiographic outcomes reaffirms the importance of phase II, dose-ranging studies in heart failure clinical trial programs. This is a critical question to address, since prescription-strength, high-dose n-3 PUFA regimens differ significantly, from the lower and inconsistent dosages found in over-the-counter supplements (some have 300 mg or less EHA/DPA per pill). In other words, simply telling patients to take “fish oil” supplements without understanding the adequacy of dosing is unlikely to yield the same benefits as promised in the current study.

One final provocative finding in the current study is the marked reduction in inflammatory cytokines achieved with the study regimen and the fact that multivariate analysis established higher baseline values of tumor necrosis factor (TNF)-alpha as a predictor of improvement in left ventricular ejection fraction. This finding is consistent with the post hoc analysis of data from GISSI-HF, which has demonstrated that circulating levels of the TNF receptor osteoprotgerin were strongly associated with the incidence of death and the composite end point of death and heart failure hospitalization (16). Whether exerting this immune-modulating effect earlier in the course of disease (as previously demonstrated in animal studies) impacts disease progression remains to be seen. Regardless, these data may suggest a potential role for the use of “inflammatory biomarkers” in selecting patients for n-3 PUFA therapy and for serving as potential biomarkers to gauge drug response. That being said, reliable inflammatory biomarkers are few and far between in the clinical setting (in fact, none of the cytokines measured are available for routine testing), and high cytokine levels are often generated in those with more advanced disease states. Defining this window of opportunity for n-3 PUFA therapy to exert its maximal effect on the natural history of heart failure is worthy of further investigation.

We continue to strive for the best supportive evidence for our treatment approaches. However in the era of personalized medicine, traditional large-scale clinical trials that have revolutionized heart failure care are unlikely to be the lone means to this end. With their concomitant need for large sample sizes and high-risk patients to achieve adequate event rates, these trial designs may be particularly inept at informing the management of specific groups of less advanced patients. This study succeeds in demonstrating how a modest treatment effect observed in a broad, unselected heart failure population can be magnified when applied to a smaller but enriched population of heart failure patients. With the fortunate hindsight of GISSI-HF, Nodari et al. (13) present a compelling test case for the dilemma facing clinicians and guideline committees alike. Would the benefits be more apparent if n-3 PUFA supplementation was given at higher doses and at earlier disease stages than that in GISSI-HF? Without a new clinical trial in sight, we are now challenged to ask ourselves whether we can be convinced to prescribe an otherwise safe and well-tolerated (but not inexpensive) drug to a broad heart failure population without the traditional strength of endorsement that large-scale pivotal studies provide, or whether future clinical effectiveness studies are needed to justify such indications. The story for n-3 PUFA s in heart failure is still being written, but it is not too early to begin to heed its lessons. Among these is the importance of opening the door for future trials in metabolic interventions to patients who are not too late in the course of their disease to benefit from what are otherwise “preventive” therapies.

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REFERENCES


**Key Words:** functional capacity • heart failure • n-3 PUFAs • nonischemic cardiomyopathy • NYHA functional class.