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Effects of supplementation with polyunsaturated fatty acids in patients with heart failure

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Abstract Despite the clinical and prognostic improvement obtained with the current medical treatment, heart failure (HF) continues to have high morbidity and mortality and its prevalence is increasing in most regions of the world. Thus, there is a need for novel adjunctive therapies that act independently of current neurohormonally and haemodynamically oriented drugs. Nutritional approaches are particularly attractive because they could work additively with established therapies without negative hemodynamic effects. There is growing evidence that omega-3 polyunsaturated fatty acids (n-3 PUFAs) supplementation positively impacts established pathophysiological mechanisms in HF and thus has a potential role for preventing and treating HF. The results of the GISSI-HF trial have indicated that, in patients with chronic HF on evidence-based therapy, long term treatment with PUFAs reduced mortality and hospitalizations for cardiovascular reasons, irrespective of etiology and left ventricular (LV) ejection fraction (EF). The purpose of this review is to summarize the evidence emerged from studies conducted so far on the effect of n-3 PUFAs in HF.

Keywords n-3 PUFAs · Heart failure · Metabolic therapy · Left ventricular function · Non-ischemic cardiomyopathy

Introduction

Heart failure is a widespread disease in the world and is estimated to affect 5 million people in the United States alone [1, 2]. Annual costs related to the treatment of HF in the United States are estimated at $38 billion, accounting for 5.4% of the healthcare budget [3]. The gold standard for treatment of HF has been based on medical guidelines published by groups such as the American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) [4–6]. The recommended pharmacological therapy includes the use of angiotensin converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs), diuretics, beta-blockers, and aldosterone antagonists. These pharmacological regimens have shown beneficial outcomes in Quality Of Life, morbidity, and/or mortality in HF patients [4]. Despite improvements in mortality, HF hospitalizations continue to rise, as an aging population lives longer secondary to increased overall life expectancy and improvements in HF therapy [7]. As more patients survive after acute myocardial infarction, thanks to improved revascularization strategies and better prevention of sudden cardiac death, they are often left with decreased LV function and HF [8]. Development of HF continues to be one of the strongest predictors of short-term readmission and mortality, with both rates remaining high despite current therapies [9]. Thus, while new medication options have improved morbidity, there remains substantial work to be done to reverse the disabling signs and symptoms of HF [10].

Over the past 30 years much epidemiological evidence and many experimental and clinical studies have supported a protective role of n-3 PUFAs in the prevention and treatment of cardiovascular diseases, particularly in coronary artery disease (CAD) and sudden cardiac death (SCD). Based on the results obtained from the GISSI-Prevenzione [11], the European Society of Cardiology and the American Heart Association (AHA) have approved n-3 PUFAs supplementation (combination of Eicosapentaenoic

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Acid, EPA, and Docosahexaenoic Acid, DHA) at a dose of 1 g/day in patients with documented CAD, also suggesting a higher dietary intake of omega-3 (at least 2 meals of fish per week) for primary prevention of cardiovascular disease in patients without documented CAD [12, 13]. PUFAs have also recently garnered increased attention in HF prevention and treatment. The purpose of this review is to summarize the evidence emerged from studies conducted so far on the effect of n-3 PUFAs in HF patients.

Omega-3 Polyunsaturated fatty acids: metabolism and biological effects in heart failure

Biochemical and biological aspects

Omega-3 are defined as essential fatty acids since they cannot be synthesized in our body, but a dietary intake, especially through oily fish (herring, mackerel, salmon, albacore tuna, sardines) or fish oil supplementation is needed [14]. There are two classes of PUFAs: omega 3 (α- linolenic acid, LNA) and omega 6 (linoleic acid, LA). Both PUFAs are metabolized to long-chain fatty acids of 20 and 22 carbon atoms: LA is metabolized to arachidonic acid (AA) and LNA to EPA and DHA. They are important components of membrane's phospholipids and at this level they compete for the same enzymatic system, since their metabolism is completely separated and their interconversion is not possible [15]. When humans ingest fish or fish oil, EPA and DHA partially replace omega 6 fatty acids, especially arachidonic acid (AA), in all cells' membrane, favorably modifying omega6/omega3 ratio. Thus a greater ingestion of EPA and DHA from fish or fish oil leads to: (1) a decreased production of thromboxane A2 leading to vasodilatation and reduction in platelet aggregation; (2) a decrease in leukotriene B4 synthesis, a powerful inducer of leukocyte chemotaxis and inflammation; (3) a decrease in cytokines levels (IL1, IL6, TNFα) with a reduced inflammatory response to endothelial and tissue damage; (4) a modulation of ionic membrane channels conduction; (5) a modulation of intracellular signal transduction and gene expression through the regulation of several transcriptional nuclear factors. [16, 17].

A large number of structural and functional abnormalities may play an important role in the pathogenesis of HF: atherothrombosis, arrhythmias, abnormalities in energy metabolism, altered expression or function of contractile proteins, abnormalities of excitation–contraction coupling, cytoskeletal abnormalities, alterations in the beta-adrenergic-receptor signal transduction, ventricular hypertrophy and remodeling, and neurohormonal-cytokine changes [18]. The clinical benefit of n-3 PUFAs may be mediated by their effects on many of these processes and mechanisms (Table 1).

Table 1 Beneficial effects of n-3 PUFAs in heart failure

Hemodynamics	Improve endothelium-dependent and independent vasodilatation
	↓ ET-1
	↑ NO
Antinflammatory	↓ NF-κB activation
	Compete with AA for COX and 5- lipoxigenase enzymatic sites
Cardiac energetics	↑ ATP generation
	↓ O2 consumption
	↓ sarcoplasmatic reticulum Ca^{2+}
Remodeling and fibrosis	↑ PPARγ → ↑ adiponectin
Vascular	↓ Platelet aggregation via ↓TXA2
	↓ VCAM-1, ELAM 1, ICAM 1
	↓ Monocyte endothelial adherence via ↓ PAF
Antiarrhythmic	↑ EPA: AA ratio in plasma membrane
	↑ Ca^{2+} –Mg^{2+} ATPase activity
	Inhibit fast voltage-dependent Na^{+} channels
	Inhibit L-type Ca^{2+}-channel

Metabolic effects: energy metabolism and mitochondrial function

Experimental data provided strong evidence that n-3 PUFAs are endogenous ligands for peroxisome proliferators activated receptors alpha and gamma (PPARα and PPARγ) [19, 20]. LV hypertrophy and enlargement induced by pressure overload are associated with a decrease in the activity of mitochondrial enzymes involved in the fatty acid oxidation and energy transduction. Omega-3 PUFAs supplementation could preserve cardiac mitochondrial function by stimulating expression of proteins involved in cardiac lipid metabolism and mitochondrial function [21, 22]. Pepe and McLennan [23] showed that isolated perfused hearts from rats fed with fish oil, in comparison with control group, had reduced myocardial oxygen consumption without a decrease in LV power generation, at low or high workload, resulting in greater LV mechanic efficiency. The mechanism for this effect is not clear, but could be due to improved mitochondrial coupling and/or a decrease in ATP hydrolysis by processes not directly related to force generation.

Anti-inflammatory effects

Persistent inflammation, involving increased levels of inflammatory cytokines and vasoconstrictor eicosanoids, seems to play a pathogenic role in chronic HF by influencing heart contractility, inducing hypertrophy and

promoting apoptosis, contributing to myocardial remodeling and to deterioration of renal function [24, 25].

The anti-inflammatory effect of n-3 PUFAs may be linked to their ability to modulate the nuclear transcription factor (NF-κB) which is activated in HF [26–28]. The PPARs activation may lead to a suppression of NF-κB and NF-κB-regulated pro-inflammatory cytokines. In a small pilot study, conducted on 14 patients with HF (NYHA class III–IV) randomized to 8 g/day of EPA and DHA, there was a reduction in cytokine (TNF-α and IL-1) levels and an improvement in the percentage of body fat, suggesting that omega-3 can decrease inflammation and prevent cachexia in advanced HF patients [29]. In a recent study the treatment with n-3 PUFAs in elderly patient with HF significantly decreased plasma levels of TNFα, IL-6, intracellular adhesion molecule 1 and NT-proBNP [30]. In another study, Eschen et al. [31] showed that n-3 PUFAs in 138 congestive HF patients did not significantly affect the plasma levels of circulating soluble cellular adhesion molecules and high sensitivity C-reactive protein, but they reduced P-selectin levels confirming their effect on platelet and endothelial activation.

In adipocytes, n-3 PUFAs from fish oil increase expression, secretion and plasma levels of the anti-inflammatory hormone adiponectin. Recent studies showed that adiponectin limits LV hypertrophy, remodeling, and contractile dysfunction in response to pressure overload and exerts anti-inflammatory effects [32]. The mechanisms for adiponectin-induced suppression of LV hypertrophy and dysfunction have been linked to activation of AMP-activated protein kinase (AMPK) [33, 34], but could also be due to inhibition of the serine–threonine kinase (Akt) [35]. However, despite the activation of AMPK by adiponectin, there is no direct clinical evidence of a strong relationship between adiponectin and HF. In the Framingham Offspring Study, adiponectin was not associated with the development of new HF, but resistin, another adipokine, resulted in a link with HF [36]. Duda et al. [37, 38] in their studies in rats showed that EPA+DHA supplementation increased adiponectin and lowered TNF-alfa serum levels in a dose-dependent manner. Anyway omega-3 supplementation did not affect the activation of AMPK or Akt, suggesting that the protective effect of adiponectin could be mediated by other mechanisms, such as the modulation of NF-κB activity.

Hemodynamic effects

Several studies have shown additional beneficial effects of n-3 PUFAs on HF development and progression by affecting hemodynamic and LV function [39]. These studies reported an improvement in endothelial function [40, 41] and a reduction in systemic vascular resistances by increasing the nitric oxide production [42, 43], a reduction in vasoconstrictive response to norepinephrine and angiotensin II, an improvement in arterial compliance and vascular response to vasodilators [44, 45]. These effects may justify the reduction of systolic (−2.1 mmHg, $p < 0.001$) and diastolic (−1.6 mmHg, $p < 0.001$) blood pressure (BP), reported in a recent meta-analysis of 36 randomized clinical trials, with an average dose of 3.7 g/day of EPA+DHA; this modest BP reduction resulted greater in older (>45 years) and hypertensive patients (BP ≥ 140/90 mmHg) [46].

Favorable effects of omega-3 administration on heart rate (HR) were also reported. A meta-analysis of 30 randomized studies showed that chronic administration of EPA+DHA (about 3.5 g/day, for a period longer than 12 weeks) can lead to a reduction in HR of about 2.5–3 beats/min in subjects with a baseline HR of 69 beats/min [47].

In addition, some experimental studies have shown that chronic administration of n-3 PUFAs can lead to an improvement in both systolic and diastolic myocardial function [48, 49] and can prevent the development of LV hypertrophy and systolic dysfunction induced by a pressure overload [38]. In a idiopathic dilated cardiomyopathy animal model, the long-term treatment with n-3 PUFAs induced a significant increase in isometric and isotonic contractile force of papillary muscles, an increase in the actin-myosin bridges [50], and a significant improvement in the peak rate of rise and fall of muscle tension, indicating a more efficient contraction and muscle relaxation, respectively [51]. These effects are probably related to the prevention of overloading of intracellular Ca^{2+} and reduction of this ion in the sarcoplasmic reticulum [52].

Antiarrhythmic effects

Tachyarrhythmias are one of the most important causes of death in patients with HF. Electrophysiological substrates of arrhythmias in HF are numerous and include LV remodeling, increased wall stress, heterogeneity of depolarization current, remodeling of ion channels and simpathovagal unbalance. Myocardial ischemia, electrolyte abnormalities, drugs, or fluctuations in the autonomic system may be the triggers [53]. Different mechanisms by which n-3 PUFAs may exert their antiarrhythmic effects have been reported, including anti-inflammatory and antithrombotic effects, modulation of ion channels (Ca^{2+} and Na^{+}) and simpathovagal balance [54–57].

The antiarrhythmic properties of n-3 PUFAs have been demonstrated in experimental models [58, 59] and in clinical trials in patients with CAD [11, 60] while the trials conducted in patients with an implantable cardioverter defibrillator (ICD) have yielded controversial results [61–

64]. These conflicting data may be due to several methodological differences regarding study population and follow-up, but the use of different formulations and doses of n-3 PUFAs may represent an important explanation. In fact, although the SCD reduction in the GISSI-Prevenzione was obtained with low dose of omega-3, it was demonstrated that the relative risk of SCD is associated with baseline blood levels of n-3 PUFAs [65] and their antiarrhythmic effects in ischemic patients with ICD are related to the increased n-3 PUFAs' concentration in cell membranes during treatment [64].

In addition, little is yet known about the impact of different etiology of HF (ischemic and non-ischemic) on the results of treatment with omega-3. In our study [66], we evaluated the effectiveness of n-3 PUFAs in reducing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy and with frequent or repetitive ventricular tachyarrhythmia episodes (NSVT), despite optimized drug therapy. At the end of the 6-month follow-up, we observed in n-3 PUFAs group, in comparison with placebo group, a significant reduction in the number and duration of episodes of NSVT ($p = 0.0002$) and a decrease of average HR of VT at Holter monitoring ($p = 0.0003$), with an improvement of heart rate variability (HRV) ($p < 0.001$) and a reduction of catecholamine and cytokine serum levels ($p < 0.001$). The n-6/n-3 PUFA ratio was significantly reduced in the treatment group from 1.12 to 3.48. As noted in other series [67, 68], the reduction in plasma levels of catecholamines and cytokines, in addition to increased HRV, were related to the increase in concentrations of EPA and DHA, confirming the impact of n-3 PUFAs on important pathogenic mechanisms of arrhythmias in non-ischemic HF patients.

n-3PUFAs in heart failure: epidemiological and interventional studies

EPA and DHA modulate favorably several factors related to the pathophysiology of HF, including the levels of fatty acids, energy metabolism of myocytes, mitochondrial function, inflammatory response and endothelial function. All these effects could contribute to prevent or delay the development and progression of HF. However, while there are more data in the literature to support a role of EPA+DHA supplementation in primary and secondary prevention of CAD [69, 70], until now there are only few evidences to support their benefit in HF patients.

Mozaffarian et al. [71] investigated the association between fish consumption and incidence of HF in the Cardiovascular Health Study, a population-based cohort study including 4,738 adults, aged >65 years. Their hypothesis was that consumption of tuna and other broiled or baked fish, but not fried fish, would be associated with a lower incidence of HF. During 12-years follow-up, 955 participants developed HF. In multivariate-adjusted analyses, tuna/other fish consumption was inversely associated with incident HF.

Another study [72] analyzed the association between fatty acid levels and HF incidence in 15,792 subjects aged between 45 and 64 years. During 14.3 years of follow-up 197 cases of HF were identified. After adjustment for age and other confounders, while the levels of saturated fatty acids (palmitic acid) were directly correlated with the incidence of HF in both sexes, levels of n-3 PUFAs showed an inverse correlation in women. Finally, Levitan et al. [73] have studied the possible correlation between HF incidence and fish consumption in a cohort of subjects aged 45–79 years in Sweden. In contrast to the study of Mozaffarian [71], the association between fish consumption and the incidence of HF showed U-shaped distribution in multivariate analysis of consumption quintiles: patients in the first quintile (0.15 g/day of fish) had a lower percentage of HF although not statistically significant (−12%) compared to no fish consumption, as well as patients in the third quintiles (0.36 g/day) had a reduced risk of HF by 33% compared to those in the fifth quintiles (0.76 g/day). The authors justify this result by assuming that subjects with a greater intake of fish could be more vulnerable to the adverse effects of fish's contaminants (mercury, dioxides) or could have more cardiovascular risk factors (hypercholesterolemia and hypertension).

The first clinical study on the administration of n-3 PUFAs in patients with HF was the GISSI-HF Investigators et al. [74]. A total of 6,975 HF patients (NYHA class II–IV) were randomized to 1 g/day of n-3 PUFAs (850–882 mg/day EPA +DHA) as ethyl ester or to matching placebo and followed for a median of 3.9 years. Results showed a significant reduction in primary endpoints, total mortality (−9%, $P < 0.05$) and mortality and hospitalizations for CV disease (−8%, $P < 0.01$) in n-3 PUFAs group in comparison with placebo, after adjustment for possible confounding factors (previous HF hospitalization, pacemaker, aortic stenosis). Although these results seem to be lower than expected, the improvement of clinical outcomes was obtained in addition to optimal medical therapy (including beta-blockers, ACE inhibitors, AT1 and aldosterone antagonists) and correspond to a NNT of 56 to prevent one death and NNT of 44 to prevent an event (death or cardiovascular hospitalization).

In addition, more recently, the results of the echocardiographic substudy of GISSI-HF evidenced that chronic administration of omega-3, in contrast to treatment with rosuvastatin, was associated with a significant increase of ejection fraction (EF) when compared to placebo (8.1 vs. 6.3% at 1 year, 11.1 vs. 8.2% at 2 years, 11.5 vs. 9.9% at 3 years, respectively; $p = 0.005$) [75]. These results

suggest that the improved survival observed in HF patients treated with omega-3 could be attributed to an improvement of LV systolic function.

Despite this evidence, no study had specifically examined the effects of omega-3 on the ventricular function and functional capacity in HF patients. To verify these effects, we enrolled 133 patients with chronic HF due to non-ischemic dilated cardiomyopathy, EF <45%, stable clinical conditions on evidence-based medical treatment at maximum tolerated target doses for at least 6 months, into a double-blind, placebo-controlled, two-arm study [76]. Participants were randomly allocated to active treatment (1.0 g gelatin capsules containing 850–882 mg of eicosapentaenoic (EPA) and docosahexaenoic (DHA) ethyl esters in the average ratio EPA/DHA of 0.9:1.5) or to placebo (1.0 g gelatin capsules containing olive oil). The treatment dose was five capsules daily for the first month followed by two capsules daily for the rest of the study. The primary outcome was the change in LV systolic function expressed as EF, while the secondary outcomes included: LV diastolic function assessed by echocardiography; functional capacity assessed by cardiopulmonary exercise testing (CPET); and NYHA functional class. At the time of enrollment and at 12-month follow-up patients underwent a physical examination, ECG, blood draw for complete blood count, comprehensive chemistry panel, inflammatory cytokines, including TNF-α, IL-6 and IL-1, and serum free fatty acids (FFAs) levels, echocardiographic study and CPET. We found that at 12 months after randomization, the n-3 PUFAs group and the placebo group differed significantly ($p < 0.001$) in regard to LV ejection fraction and the other echocardiographic variables and in parameters of functional capacity. In particular, the n-3 PUFA group showed, at 1 year of follow-up compared with baseline, a significant increase in EF (10.4 ± 9.5%, $p < 0.001$) (Fig. 1), a significant reduction in diameter (EDD −1.8%, $p < 0.0001$; ESD −4.5%, $p < 0.001$) and ventricular volume (EDV −2.5%, $p < 0.001$; ESV −7.5% $p < 0.0001$). In contrast, in the placebo group at the end of the study there was a significant reduction in EF as well as a statistically significant increase in ventricular diameters and volumes. In the group treated with n-3 PUFAs was also observed an improvement of diastolic function was also observed, expressed by a significant reduction of diastolic dysfunction score (−4.74%, $p = 0.004$) compared with an increase in this parameter in the placebo group (10.1%, $p < 0.001$). Positive results of treatment with omega-3 were observed for the functional capacity, expressed by an increase of peak VO2 (6.2%, $p < 0.001$) and duration of exercise (7.7%, $p < 0.001$) to cardiopulmonary stress test and a reduction in NYHA functional class (from 1.88 ± 0.33 to 1.61 ± 0.49, $p < 0.001$). In the placebo group was shown at 12-month follow-up to a greater

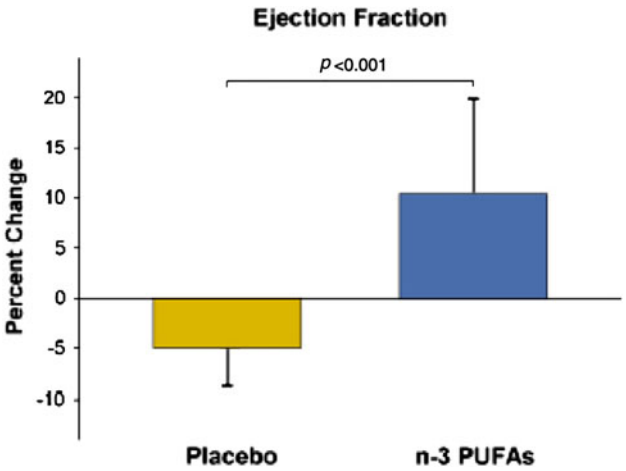

Fig. 1 Variations of the EF in the two study groups (from Nodari [76])

degree of functional impairment was shown at a decline in oxygen consumption and an increase in NYHA class. During follow-up, the serum levels of inflammatory cytokines (TNF-alpha, IL-6, IL-1) increased significantly in the placebo group, while decreased in omega-3 group ($p < 0.001$). Of interest, throughout follow-up, lower hospitalization rates for cardiovascular causes (15 vs. 39%, respectively; $p = 0.002$) and for HF (6 vs. 30%, respectively; $p = 0.0002$) were noted in the n-3 PUFAs-treated patients compared to those on placebo ($p < 0.0002$). The results of our study suggest that n-3 PUFAs may act favorably on ventricular function, both systolic and diastolic, on left ventricular remodeling and functional capacity, resulting in a lower incidence of HF and cardiovascular hospitalizations.

Dose and optimal ratio of DHA/EPA

The potential favorable mechanisms of n-3 PUFAs in CV diseases seem closely related to increased concentrations of EPA and DHA in cell membranes [77]. The antiplatelet, anti-inflammatory and lipid-lowering effects occur with relatively high doses of EPA and DHA (3–4 g/day); on the other hand the antiarrhythmic effect, the prevention of SCD and the improvement in HF can be achieved with lower doses (500–1,000 mg/day). The optimal dose and the ratio of DHA and EPA has not been defined yet. DHA and EPA are found in most kinds of fishes, particularly in fatty fishes, usually in a 2:1 ratio, while pharmacological preparations typically have a ratio of 2:3 or less [78]. Moreover, while the administration of DHA can also increase levels of EPA, the reverse process from EPA to DHA in humans does not occur [79]. DHA is more represented than EPA in myocyte membrane and its administration (alone or in

combination with EPA) seems to be more effective than only EPA in preventing arrhythmias and SCD. Although the beneficial effects on arrhythmias occurred at low doses, the relative risk of SCD was inversely correlated with baseline blood levels of n-3 PUFAs and protective effect in patients at high risk of fatal arrhythmias, such as ICD patients, was correlated with the concentration achieved during treatment [64]. Similarly, an inverse correlation was confirmed between tissue levels of DHA and CAD [80]. A recent study [81] conducted in patients with HF showed an association between DHA concentrations and degree of LV remodeling: for diastolic diameter between 68 and 90 mm (upper tertile) compared with diameters between 48 and 61 mm (lower tertile), as well as EF values between 9 and 25% (lower tertile) compared with values of EF from 35 to 50% (upper tertile), serum concentrations of DHA were significantly lower (1 vs. 1.3%, $p < 0.001$).

In our studies [77] we observed a significant inverse association between baseline levels of omega-3 (particularly DHA) and magnitude of LV remodeling and dysfunction, and between increased concentrations of DHA and the improvement in these parameters at the end of follow-up. These results suggest a prominent role of DHA in the pathophysiology and then in the treatment of ventricular dysfunction and remodeling.

As part of a therapy "tailored" for each patient, DHA could be a new sensitive biomarker for monitoring and diagnosis of systolic dysfunction and dilation in patients with LV systolic HF, or could be used to determine the optimal dosage and to monitor the response to therapy in each patient.

Conclusion and future perspectives

In recent years there has been increasing evidence from observational, experimental and clinical studies about the beneficial effects of omega-3 in the prevention and treatment of cardiovascular disease and their possible mechanisms of action. However, sometimes conflicting results have raised doubts and uncertainties. This is partly motivated by the insufficient knowledge about the role of omega-3 in complex biological mechanisms and cellular system and by the publication of studies which seem similar, but have significant differences in methodology (case studies, dose, duration of follow-up, etc.) which can lead to different results.

The GISSI-HF has not only provided important evidence concerning the improvement of prognosis in patients with HF treated with omega-3, but it also raised many questions about the mechanisms underlying the favorable effect of n-3 PUFA in HF, in which patient could have more benefit from the treatment with n-3 PUFA and which is the optimal dose. In our experience, the n-3 PUFA supplementation in addition to an optimized medical therapy, was associated not only with a reduction of arrhythmic risk, but also to an improvement in EF and functional capacity, important prognostic factors in HF patients.

Targeted studies are needed to respond to specific questions, first the optimal dose to use and the optimal ratio of EPA and DHA. The history of n-3 PUFAs in HF is definitely still developing, but it is not too early to start listening to its lessons. Among these, for example, there is the importance of undertaking studies on the effects of metabolic therapy in patients with advanced-stage of HF, in which therapeutic intervention may help to recover dysfunctional, but vital, myocardium.

Conflict of interest None.

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