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Omega-3 supplementation and outcomes of heart failure

A systematic review of clinical trials

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Abstract

Backgrounds: Omega-3 supplements are endorsed for heart failure (HF) patients to reduce hospitalizations and mortality, offering anti-inflammatory and cardioprotective benefits.

Methods: A comprehensive search was conducted in various databases until November 2022. Eligible studies included clinical trials on patients with HF. Data extraction covered study details, omega-3 specifics, outcomes, and limitations. The JADAD scale was used to assess the risk of bias in randomized controlled trials.

Results: The review process involved 572 records from database searches, resulting in 19 studies after eliminating duplicates and screening. These studies assessed the impact of omega-3 on various clinical outcomes, such as mortality, hospitalization, cardiac function, and quality of life. Studied duration varied from weeks to years. Omega-3 supplementation demonstrated potential benefits such as improved heart function, reduced inflammation, and decreased risk of cardiovascular events.

Conclusion: Omega-3 supplementation could benefit heart disease treatment, potentially reducing therapy duration and improving outcomes. Starting omega-3 supplementation for HF patients seems favorable.

Abbreviations: BNP = brain-type natriuretic peptide, CHF = chronic heart failure, CVDs = cardiovascular diseases, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, HF = heart failure, HR = heart rate, hs-CRP = high sensitivity C-reactive protein, ICAM-1 = intercellular adhesion molecule 1, IL-6 = interleukin-6, LV = left ventricle, LVEF = left-ventricle ejection fraction, MCP-1 = monocyte chemotactic protein-1, MI = myocardial infarction, n-3 PUFAs = omega-3 polyunsaturated fatty acids from marine sources, NPs = natriuretic peptides, NT-proBNP = N-terminal pro-B-type natriuretic peptide, QoL = quality of life, TNF-α = tumor necrosis factor alpha, ω-3 PUFAs = omega-3 polyunsaturated fatty acids.

Keywords: dietary supplements, fatty acids, heart failure, omega-3, outcomes, systematic review

MN, MEH, AA, and AT contributed equally to this work.

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1. Introduction

Heart failure (HF) is now a worldwide epidemic, with its prevalence and incidence increasing at a fast pace.[1] According to the American Heart Association data, 8.1 million individuals in the United States are currently suffering from this condition. By 2030, it is anticipated that the global incidence of HF will rise by 46%, emerging as a significant global health concern.[1] The World Health Organization (2016) has categorized HF as a major contributor to mortality in Europe, pinpointing diet, physical inactivity, smoking, alcohol consumption, hypertension, high cholesterol levels, excess weight, obesity, and diabetes as the primary risk factors.[1] HF is a consequence of various cardiovascular diseases (CVDs) and continues to be linked with a reduced quality of life (QoL), early mortality, and significant utilization of healthcare resources.[2–5] Despite the recent advancements in both pharmaceutical and interventional treatments, HF remains a leading cause of mortality and recurrent hospitalization.[6,7] It also serves as a predictor of lethality among geriatric patients.[8] Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have emerged as a vital category of dietary lipids that have demonstrated cardiovascular protective properties in HF patients.[3,9]

Omega-3 polyunsaturated fatty acids obtained from marine sources (n-3 PUFAs), specifically Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have shown effectiveness in managing HF. Among the numerous nutraceuticals that have been studied for their potential impact on HF outcomes, only ω-3 PUFAs have received a favorable recommendation in the Australian HF guidelines.[10]

Omega-3 fatty acids have shown an association with reducing myocardial fibrosis, left ventricular remodeling, and lowering systemic inflammation after myocardial infarction (MI). Additionally, significant decreases in events such as nonfatal MI, nonfatal stroke, cardiovascular-related deaths, coronary revascularization procedures, and unstable angina have been documented.[6] These findings carry particular importance since persistent inflammation is a significant contributor to the development of HF.[7,11,12] The most significant findings came from studies evaluating the impact of EPA/DHA supplementation on HF and other CVDs.[13] The researchers revealed the effectiveness of n-3 PUFA supplementation in preventing CVD events, such as HF and MI, with a particularly strong protective effect observed at higher dosage levels. However, accurately assessing the beneficial effects of n-3 PUFAs in clinical trials focusing on heterogeneous conditions like HF poses challenges. Several variables (e.g., race, age, sex, and dose of EPA/DHA) can influence the clinical outcomes in these trials. In addition, given the diverse effects of n-3 PUFAs in vivo, understanding their pathophysiologic effects on HF remains a complex endeavor.

Significant benefits associated with the utilization of omega-3 in individuals with HF have been identified. Research has shown that omega-3 can lower the rate of patient readmissions.[14,15] Additionally, some studies have found that omega-3 supplementation can reduce mortality.[16,17] Multiple articles have confirmed the anti-inflammatory properties of omega-3.[16,18,19] Moreover, a limited set of studies has suggested that omega-3 supplementation may positively impact the QoL by ameliorating depressive symptoms among HF patients.[20–22] However, further investigations are necessary to draw a definitive conclusion.

So far, several review studies have been undertaken regarding the effects of omega-3 on HF. These studies have assessed only a few outcomes, such as mortality and hospitalization.[16,19,23] They also reviewed the physiological effects and mechanism of omega-3 in HF patients.[16,19,23] However, clinical research has suggested that omega-3 may have an impact on a range of other HF-related outcomes. These include MI, stroke,[24,25] revascularization, and cardiac function in HF,[26,27] which have not been considered in previous studies.[13,14] In addition, the use of complementary and alternative medicine, which includes dietary supplements for preventing and treating illness, is a multibillion-dollar industry. Patients with HF commonly resort to complementary and alternative medicine, even without substantial evidence. Generally, there is inadequate high-quality evidence to support the significant therapeutic impact of these therapies.[28] Therefore, for the first time, we aimed to offer a comprehensive systematic review encompassing various outcomes associated with omega-3 supplementation among patients with HF, which helps clinicians be aware of the potential effects of omega-3 supplementation on improving HF outcomes. On the other hand, it allows researchers to be aware of the knowledge gaps and to consider them through further trials.

2. Methods

2.1. Data sources and searches

In this systematic review, we conducted a comprehensive search from its inception to November 2022. Our search encompassed various databases, including PubMed, Web of Science Conference Proceedings Citation Index, Scopus, and Open Access Thesis and Dissertations. Initially, we developed a search strategy within the PubMed database. This strategy consisted of the following search terms: ((“fish oil” OR “fish liver oils” OR “cod liver oil” OR “omega 3 fatty acid” OR “eicosapentaenoic acid” OR “icosapentaenoic acid” OR “eicosapentaenoate” OR “docosahexaenoic acid” OR “docosahexaenoate”) AND (“heart failure” OR “Cardiac failure” OR “Congestive heart failure” OR “heart decompensation”) (. Subsequently, this strategy was adapted for use in other electronic databases without date and language restrictions. A detailed representation of this adaptation can be found in Table S1, Supplemental Digital Content, http://links.lww.com/MD/L225.

2.1.1. Study selection. Three authors (MN, MH, HG) reviewed and retrieved all studies independently to determine their suitability for inclusion in the study based on their titles and abstracts. Then, the full texts of the papers were evaluated, and studies were selected according to the predetermined eligibility criteria.

The eligibility criteria were: clinical trial studies and adult patients with HF at any stage. Any disagreements resolved by the fourth author (HN) through discussion and adjudication. Consequently, observational studies, case reports, case series, newspaper articles, magazine articles, or commentaries were excluded from the review process. Articles without abstract, full-text, or sufficient relevant data were likewise excluded from the analysis.

2.1.2. Data extraction. The data extraction form captured the following variables: first author name, publication year, study country, design, population, the dose and type of omega-3, measured outcomes, obtained results, and study limitations. In cases where the required data was not found in the included studies, the authors made multiple attempts to contact the corresponding authors to obtain the missing data or seek clarification. If the authors did not receive a response after 3 communication attempts, the study was excluded from the analysis.

2.1.3. Risk of bias assessment. To assess the risk of bias in included studies, we used the JADAD scale for reporting randomized controlled trials,[29] which was assessed by 2 independent authors (MN, AT). Any disagreements were resolved by discussing and consulting with a third person (SSK) to reach a consensus. The quality score ranged between 0 and 5, of which 0 to 2 was considered low quality, 3 was medium quality, and 4 to 5 was high quality.

4.2.1.. Synthesis methods. Due to variation in the study outcomes and methodological heterogeneity, all study combination was not provided. Therefore, we presented study characteristics, findings, and limitations through a table.

3. Results

The process of searching, screening, and selecting studies for this review is demonstrated in Figure 1. Initially, 572 records were identified through electronic database searches. After removing duplicates and excluding records based on title and abstract screening, the full texts of 32 studies were assessed, and finally, 19 out of 33 studies were included in this review (Fig. 1).

The characteristics of the included studies are listed in Table 1. These studies evaluated the effect of omega-3 on clinical outcomes, including mortality, hospitalization, MI, cardiac function, arrhythmias, inflammatory markers, and lipid profiles, and the patient-reported outcomes such as QoL and depression (Fig. 2).

Table 2 indicates the quality assessment of included studies using the JADAD scale. According to this table, most of the studies had medium quality. Although the majority of studies used randomization to allocate the intervention to the study groups, the method of randomization was not explained in

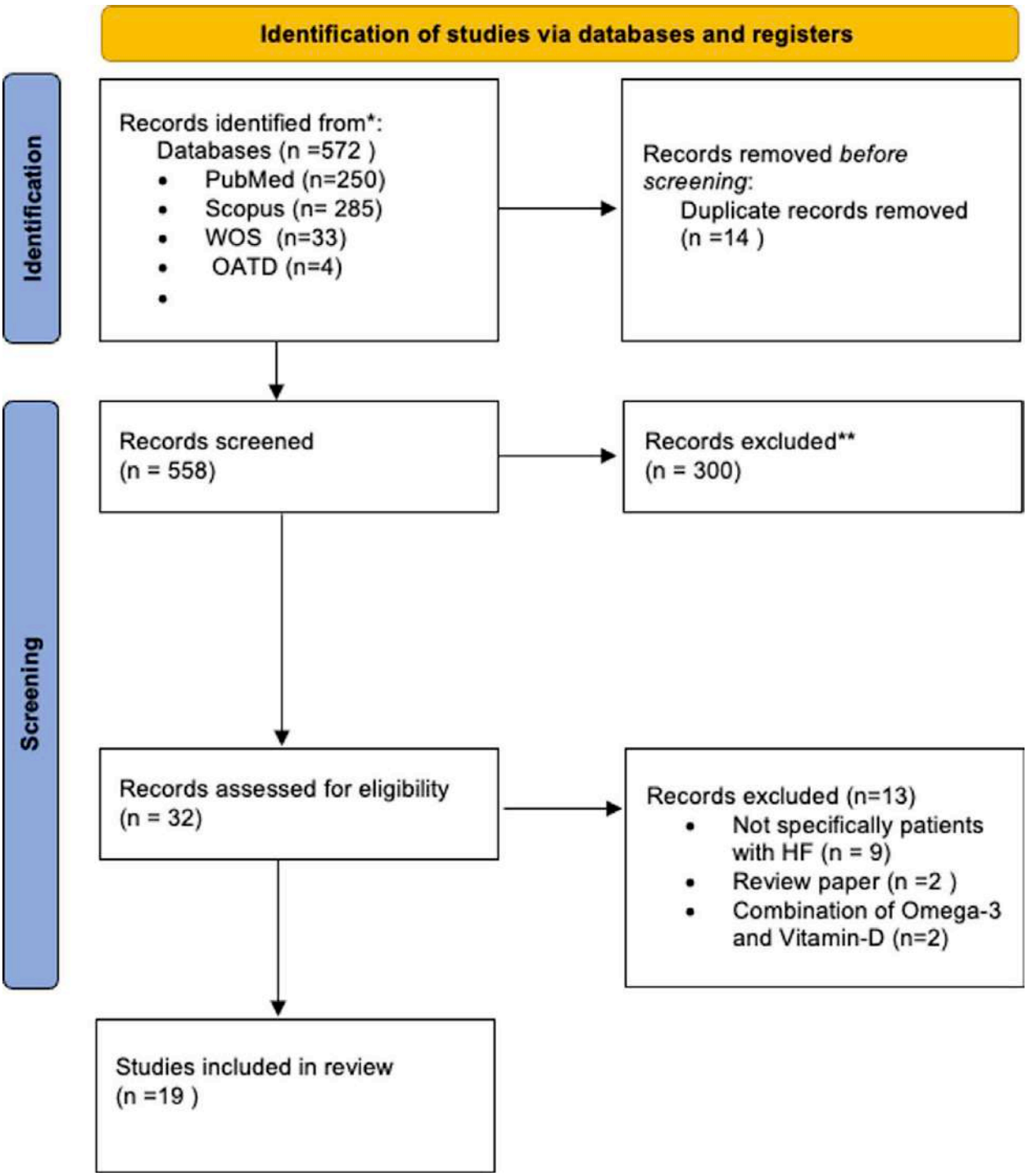

Figure 1. PRISMA 2020 flow diagram of searching, screening, and selecting the records.

Table 1

The characteristics of included studies in the review.

References	Country	Population	Design	Intervention	Comparison	Duration of intervention/ follow-up	Primary outcome (s)	Key findings	Limitations
Radaelli et al (2006)[30]	Italy	•n = 15 PUFA •n = 10 Placebo •Patients with chronic post-MI systolic HF •LVEF < 40%	Randomized, controlled trial	•2 g/d PUFA (contacting EPA/DHA ratio of 0.9–1.5)	Placebo	4 mo	Cardiac function, Inflammatory markers, BP	Dietary PUFA supplementation enhances HR variability in patients with stable congestive HF	•Fatty acid concentrations were determined only at the end of the study •Limited study size
Mehra et al (2006)[31]	USA	•n = 7 n-3 fatty acids •n = 7 Placebo •Patients with severe HF •Age 48–74 yr •NYHA class III–III	Randomized, double-blind, placebo trial	•8 g/d n-3 fatty acids •n-3 fatty acid content of 1 g of the n-3 ethyl ester (consist of 80% n-3 fatty acid ethyl esters) (44% EPA, 24% DHA, 12% other n-3 fatty acid ethyl esters)	4 capsules Iso-caloric corn oil placebo, twice daily	18 wk	Cardiac function, inflammatory marker, TNF- and interleukin-1 (IL-1) production	Fish oils therapy: decrease TNF-a production in HF, improve body weight, represent a novel therapeutic approach in late-stage HF characterized by cardiac cachexia	•Small number of patients •Short follow-up time
O'Keefe et al (2006)[32]	USA	•n = 18 •White men with history of MI (3 mo to 5 yr previously), and a stable medical regimen •LVEF < 40%	Randomized, placebo-controlled, double-blind, cross-over trial	•3 Capsules/d containing 225 mg of EPA + 585 mg of DHA	Placebo contained a 50:50 mix of corn and olive oils	2 sequential 4-mo periods	Cardiac function, hospitalization, inflammatory markers	There were no significant effects on BP, arterial compliance, lipids, or inflammatory markers	Not mentioned
Morgan et al (2006)[33]	UK	•n = 20 •Patients with CHF •Age ≥ 65 yr •NYHA class II–III •LVEF < 40%	Randomized, double blind cross-over trial	•10 mL/d omega-3 fatty acids (high-strength cod liver oil, Seven Seas, Hull, United Kingdom)	10 mL/d Olive oil (in identical bottles) as placebo	Three 6-wk phases	Endothelium-independent vasodilation-, Forearm blood flow (FBF)	Dietary omega-3 supplementation was accompanied by an increase in FBF response to ACH, which represents enhanced endothelium-dependent vasodilation in CHF	Not mentioned
Del Turco et al (2008)[34]	Italy	•n = 23 5.2 g of n-3 fatty acids •n = 23 Placebo •Patients discharged from the Department of Cardiology at Aalborg Hospital after MI •Age ≤ 75 yr •LVEF < 40%	Randomized, placebo-controlled, open-label trial	•5.2 g/d n-3 fatty acids (corresponding to 4.3 g of EPA and DHA, given as 8 capsules)	Olive oil as placebo	12 wk	Circulating microparticles, tissue factor antigen, platelet- and monocyte	Treatment with n-3 fatty acids after MI exerts favorable effects on levels of platelet- and monocyte-derived microparticles.	•Not mentioned

(Continued)

Table 1

(Continued)

References	Country	Population	Design	Intervention	Comparison	Duration of intervention/ follow-up	Primary outcome (s)	Key findings	Limitations
Tavazzi et al (2008)[7]	Italy	•n = 3494 n-3 PUFA •n = 3481 Placebo •Patients with clinical evidence of HF of any cause •Age ≥ 18 yr •NYHA class II–IV •Irrespective to LVEF	Multicenter, randomized, placebo-controlled, double-blind trial	•1 g/d n-3 PUFA •n-3 PUFA containing 850–882 mg EPA and DHA in the average ratio of 1:1.2	10 mg/d rosuvastatin or corresponding placebo	Follow-up time: Median (IQR): 3.9 (3–4.5) yr	Time to death, and time to death or admission to hospital for cardiovascular reasons	Treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular disease	•Not mentioned
Zhao et al (2009)[35]	China	•n = 38 n-3 PUFA •n = 37 Placebo •Patients with symptoms of HF (secondary to ischemic or IDC) on optimal medical treatment •Age ≥ 60 yr •NYHA class II–III •LVEF < 40%	Placebo-controlled, single-blind trial	•2 g/d n-3 PUFA n-3 PUFA (containing 180 mg EPA and 120 mg DHA per g of n-3 PUFA)	Placebo	3 mo	Circulating inflammatory markers and NT-proBNP	Changes by n-3 PUFA in levels of NT-proBNP, TNF-α, IL-6 and ICAM-1 were significantly higher than placebo group	•Small sample size •Short duration
Nodari et al (2009)[36]	Italy	•n = 22 n-3 PUFAs • n = 22 Placebo •Patients with IDC with a normal CAG, with no ischemic episodes, stable clinical and hemodynamic conditions for at least 3-mo, with an optimal medical treatment •NYHA class II–III •LVEF ≤ 45%	Randomized, double-blind trial	•Five capsules/d for the 1st mo •1 Capsule/d of n-3 PUFA for the following mo n-3 PUFA (containing 850–882 mg of EPA and DHA ethyl esters in the average ratio EPA/DHA of 0.9:1.5)	1 g capsules of olive oil as placebo	6 mo	Arrhythmic, ECG, HR, catecholamine and cytokine plasma levels	n-3 PUFA is associated with favorable effects on parameters related to arrhythmic risk in patients with IDC	•Single center study •Small sample size
Ghio et al (2010)[37]	Italy	•n = 312 n-3 PUFA •n = 296 Placebo •n = 212 Rosuvastatin •n = 207 Placebo •Patients with symptomatic HF of any cause, already on treatment •NYHA class II–IV	Multi-center, randomized, placebo controlled, double-blind trial	•1 g/d n-3 PUFA •10 mg/d Rosuvastatin	Placebo	3 yr	LVEF and hospital admission	LVEF increased with n-3 PUFA at 1 yr, 2 yr, and 3 yr vs the placebo group which was paralleled in the n-3 PUFA group by a reduced number of deaths and by a reduced number of hospital admissions	•Plasma levels of inflammatory markers were not measured to explain pathophysiological mechanisms underlying the effects of n-3 PUFA on LV function

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Table 1

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References	Country	Population	Design	Intervention	Comparison	Duration of intervention/ follow-up	Primary outcome (s)	Key findings	Limitations
Eschen et al (2010)[38]	Italy	•n = 69 n-3 PUFAs •n = 69 Placebo (olive oil) •Patients with CHF caused by IHD or DCMP with oral medication for at least 3 mo prior to study •Age 19–80 yr •NYHA class II–III •LVEF < 40%	Multi-center, randomize placebo controlled, double-blind trial	•0.9 g •n3-PUFA (EPA and DHA as ethyl ester)	1 g of olive oil as placebo	24 wk	Inflammatory markers	A daily supplement does not significantly affect plasma levels of sCAMs or hs-CRP	Small study size
Nodari et al (2011)[6]	Italy	•n = 67 n-3 PUFAs •n = 66 Placebo •Patients with a diagnosis of NICM and stable clinical conditions •Age 18 to 75 yr •NYHA class I–II •LVEF ≤ 45%	Randomized, placebo-controlled, double-blind trial	•1 g/d n-3 PUFAs for the 1st mo •2 g/d for rest of the study n-3 PUFAs (containing 850 to 882 mg of EPA and DHA in average ratio of 0.9:1.5)	1 g capsule of placebo (olive oil)	12 mo	Change in LV systolic function	PUF as treatment increases LV systolic function and functional capacity and may reduce hospitalizations for HF	•Single-center small study •Diastolic function Evaluation did not include tissue Doppler measurements •Results cannot be generalized to HF patients with a different etiology and/or at more advanced stages
Moertl et al (2011)[39]	Austria	•n = 12 1g n3-PUFA •n = 12 4g n3-PUFA •n = 12 Placebo •Patients with severe CHF •NYHA class III–IV •LVEF < 35%	Randomized-placebo-controlled 3-arm, double-blind trial	•1g/d •4g/d n3-PUFA •(Containing 850–882 mg EPA and DHA as ethyl esters in the average ratio of EPA/DHA 1:1.2)	Placebo	12 wk	Markers of platelet activation and Inflammatory markers	Treatment with n-3 PUFA decreases platelet activation and tissue factor in a dose-dependent fashion	•Small sample size
Moertl et al (2011)[40]	Austria	•n = 14 1 g/d n3-PUFA •n = 13 4 g/d n3-PUFA •n = 14 Placebo •Patients with CHF nonischemic origin •NT-proBNP > 2000 pg/mL •Age ≥ 18 yr •NYHA class III–IV •LVEF ≤ 35%	Randomized 3-arm, placebo-controlled, double-blind trial	•4 g/d n3-PUFA (4 capsules Omacor) •1 g/d n3-PUFA (1 capsule Omacor and 3 placebo capsules) •n-3 PUFA (at least 900 mg of omega-3 acid ethylesters as a combination of EPA) (approximately 465 mg) and DHA (approximately 375 mg)	4 capsules as Placebo, taken as 2 capsules twice/d	12 wk	Changes in LVEF, plasma high-sensitive IL-6 and high-sensitive TNF-α, and peak VO2	Treatment with n3-PUFA increase of LVEF A significant improvement of endothelial function (TNF-α) and decrease of IL-6 is found with high-dose n3-PUFA intervention No changes in VO2 peak were found	•Small sample size •Highly selected study population limits study generalizability

(Continued)

Table 1

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References	Country	Population	Design	Intervention	Comparison	Duration of intervention/ follow-up	Primary outcome (s)	Key findings	Limitations
Kojuri et al (2013)[41]	Iran	• n = 38 Omega-3 •n = 32 Placebo •Patients with CHF who had a tri-chamber pacemaker and automated defibrillator •NYHA class II–III •LVEF ≤ 40%	Single-center, randomized, placebo-controlled double-blind trial	•2 g/d Omega-3 fatty acid (2 capsules/d each containing 1000 mg)	2 placebo capsules contained distilled water with color of omega-3 capsules, twice/d	6 mo	Plasma BNP levels, echocardiography parameters, 6-min walk test	Omega-3 supplementation can result in small changes in plasma BNP levels and modest improvements in echocardiographically assessed diastolic function About average distance walked, no significant increase was omega-3 group compared to the placebo group	•Small sample size •Single center study with short follow-up time
Kohashi et al (2014)[42]	Japan	•n = 71 EPA group •n = 68 No EPA groups •Patients with CHF who had been stabilized by standard medical therapies for CHF •Mean (SD) age 70.2 (9.0) yr •Mean (SD) LVEF of 37.6 (8.0) %	Non-randomized clinical Trial	•1800 mg/d •EPA	No EPA group	Median follow-up 28 mo (Range: 12–60 mo)	The monocyte chemoattractant protein (MCP-1), asymmetric dimethylarginine (ADMA) levels, and LVEF	In the EPA group, LVEF had improved, and MCP-1 and ADMA levels had decreased	•Small sample size •EPA was not assigned in a randomized manner •This study limited to stabilized patients with CHF •The dietary intake of fish and Omga-3 PUFA was not determined
Chrysohoou et al (2016)[43]	Greece	•n = 95 1000 mg omega 3-PUFAs •n = 110 No omega 3-PUFAs •Patients with chronic compensated HF, due to ischemic or dilated cardiomyopathy • NYHA class I–III •LVEF < 40%	Randomized, open label clinical trial	•1000 mg omega 3-PUFAs supplementation	No omega 3-PUFAs supplementation	6 mo	Echocardiographic assessment and Plasma BNP	Omega 3-PUFAs supplementation was associated with improved left diastolic function and decreased BNP levels	•The study size may not be sufficient for detecting differences •Absence of blindness might led to overoptimistic results •Limited generalizability due to single center study
Jiang et al (2018)[22]	USA	•n = 36 High EPA •n = 36 EPA/DHA •n = 36 Placebo •Patients with clinical diagnosis of CHF and diagnosis of MDD with a Hamilton Depression Scale score ≥ 18 •Age ≥ 18 yr •NYHA class II–IV	Multi center randomized, double-blind, placebo-controlled pilot clinical trial	•4 capsules of almost pure EPA 500 mg per capsule ("high EPA") daily for 12 wk 4 capsules of 400/200 EPA/DHA 500 mg per capsule ("2:1 EPA/DHA") daily for 12 wk	4 capsules of corn oil ("placebo"), daily for 12 wk	12 wk	Red blood cell, Depression, Quality of life	Omega-3 supplementation resulted in significant increases in omega-3 levels in red blood cell counts Changes in cognitive depressive symptoms and social aspect of quality of life were in favor of the omega-3 supplementation	•It was not sufficiently powered to detect the small effect sizes of antidepressant agents or psychotherapy for MDD •Multiple testing and its correction were not considered

(Continued)

Table 1

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References	Country	Population	Design	Intervention	Comparison	Duration of intervention/ follow-up	Primary outcome (s)	Key findings	Limitations
Wurm et al (2018)[44]	Austria	•n = 12 1 g n3-PUFA •n = 12 4 g n3-PUFA •n = 16 Placebo •Patients with advanced HF of non-ischemic origin who were on stable optimized medical therapy for ≥ 3 mo •NT-proBNP levels of > 2000 pg/mL •NYHA class III or IV •LVEF < 35%	Randomized, double-blind, placebo-controlled trial	•1 g/d n3-PUFA for 12 wk •4 g/d n3-PUFA for 12 wk	Placebo for 12 wk	12 wk	Anti-oxidant function of HDL	Results showed adverse effect of n3-PUFA supplementation on anti-oxidant function of HDL	•Small sample size •Single center study •Limited to patients with HF of nonischemic origin
Selvara et al (2022)[45]	USA	n = 703 Icosapent ethyl n = 743 placebo Patients with a history of HF NYHA CLASS I–III	Randomized, clinical trial	•Icosapent ethyl	Placebo	Median follow-up duration of 4.6 yr	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Similar improvements provided by icosapent ethyl in triglyceride levels and hs-CRP as well as similar cardiovascular risk reduction in patients with and without HF	•Lack of data on ejection fraction •History of HF at baseline was based on report and not verified by additional criteria

ACH = acetylcholine, ACS = acute coronary syndromes, AF = atrial fibrillation, AICD = automatic implantable cardiac defibrillator, ANP = atrial natriuretic peptide, BNP = brain-type natriuretic peptide, BUN = blood urea nitrogen, CHD = coronary heart disease, CHF = chronic heart failure, CRT = cardiac resynchronization therapy, DCMP = dilated cardiomyopathy, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EF = ejection fraction, EPA = eicosapentaenoic acid, FMD = flow-mediated vasodilation, HDL-C = high-density lipoprotein cholesterol, HF = heart failure, HR = heart rate, hs-CRP = high sensitivity C-reactive protein, ICAM-1 = intercellular adhesion molecule 1, ICD = implantable cardioverter defibrillator, IDC = idiopathic dilated cardiomyopathy, IHD = ischemic heart disease, IL-1 = interleukin-1, IL-6 = interleukin-6, Int. group = intervention group, LDL = low-density lipoprotein, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVEF = left-ventricle ejection fraction, LVESD = left ventricular end-systolic diameter, MCP-1 = monocyte chemotactic protein-1, MI = myocardial infarction, n-3 PUFAs = omega-3 polyunsaturated fatty acids from marine sources, NICM = nonischemic dilated cardiomyopathy, NIHF = nonischemic heart failure, NSVT = non-sustained ventricular tachycardia, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, PSA = power spectral analysis, SAECG = signal averaged ECG, sCAMs = soluble cellular adhesion molecules, sICAM-1 = soluble intercellular adhesion molecule-1, sP-selectin = soluble P-selectin, SS = sample size, sVCAM-1 = soluble vascular adhesion molecule-1, TNF-α = tumor necrosis factor alpha, VCAM-1 = soluble vascular cellular adhesion molecule 1, VF = ventricular fibrillation, VPBs = ventricular premature beats, VT = ventricular tachycardia.

most of them. In addition, most of the studies did not mention how blinding was applied. However, all studies determined the patients' outcomes.

4. Discussion

This review reviewed a range of outcomes considered in clinical trials following omega-3 supplementation, including clinical outcomes such as mortality, hospitalization, MI, cardiac function, arrhythmias, inflammatory markers, and lipid profiles, patient-reported outcomes such as QoL and depression (Fig. 2).

4.1. Mortality

HF has been recognized as a global public health concern.[52] It exhibits a 1-year mortality rate of 24% in adults and 33% across all age groups, surpassing the mortality rates of numerous prevalent chronic illnesses like cancer.[53] Different interventions were conducted to reduce the mortality of patients with HF. A review by Ruppar et al determined that educational interventions aimed at improving treatment adherence reduced mortality among HF patients.[17] Feltner observed that Home-visiting programs at 30 days also reduced HF mortality rates and can prevent adverse outcomes.[54] Further studies revealed that the absence of crucial nutrients and essential mineral materials can increase mortality rates or disturb the treatment process.[55] A systematic review and meta-analysis conducted by Angkananard et al in 2016 established an association between serum magnesium levels and mortality outcomes among HF patients. Their findings indicated a noteworthy connection between elevated magnesium levels, defined as serum Mg ≥ 1.05 mmol/L, and an increased mortality risk.[56]

Additional research indicates that modifying the diets of individuals with HF can yield positive clinical outcomes, enhance treatment responses, and decrease mortality rates.[57] The DASH trial, for example, showed the beneficial effects of adopting a healthy diet in mitigating the risk of high blood pressure. Moreover, emerging evidence suggests that incorporating marine omega-3 fatty acids into one diet may lower the likelihood of HF-related fatalities.[58]

Our review of various studies found that consumption of omega-3 fatty acids could effectively reduce HF mortality.[7] A study by Tavazzi et al showed that n-3 PUFA provides some benefits in terms of all-cause mortality rates as a simple and safe therapeutic approach.[7]

Research exploring the impact of ω-3 PUFAs on mortality related to various diseases has yielded mixed results.[28] One set of studies found that higher levels of omega-3 PUFA were linked to a notable reduction in the risk of CVDs, coronary heart disease, and overall mortality.[59] A study conducted by Harris et al in 2021 established that elevated blood n-3 fatty acid levels were connected to a decreased risk of death.[60] However, despite numerous investigations into this matter,

Figure 2. Effect of omega-3 supplementation on the outcomes of patients with heart failure.

Table 2

Quality assessment of included studies using the JADAD scale.

	Randomization		Blinding				
Author (yr)	Yes/no	Method	Yes/no	Method	An account of all patients (score)	Total JADAD score	Qualitative rating*
Radaelli (2006)[43]	1	0	0	0	1	2	Low
Mehra (2006)[46]	1	0	1	0	1	3	Medium
O'Keefe (2006)[40]	1	0	1	0	1	3	Medium
Morgan (2006)[31]	1	0	1	0	1	3	Medium
Turco (2008)[38]	1	0	0	0	1	2	Low
Tavazzi (2008)[7]	1	1	1	1	1	5	High
Zhao (2009)[39]	1	1	1	1	1	5	High
Nodari (2009)[41]	1	0	1	0	1	3	Medium
Ghio (2010)[47]	1	0	1	0	1	3	Medium
Eschen (2010)[48]	1	0	1	0	1	3	Medium
Nodari (2011)[6]	1	0	1	1	1	4	High
Moertl (2011)[45]	1	0	1	0	1	3	Medium
Moertl (2011)[49]	1	0	1	1	1	4	High
Kojuri (2013)[42]	1	1	1	0	1	4	High
Kohashi (2014)[32]	0	0	1	1	1	3	Medium
Chrysohoou (2016)[35]	1	1	0	0	1	3	Medium
Jiang (2018)[22]	1	1	1	0	1	4	High
Wurm (2018)[50]	1	1	1	0	1	4	High
Selvaraj (2022)[51]	1	0	0	0	1	2	Low

*Total scores 0–2 was considered low quality, 3 was considered medium quality, and 4–5 was considered high quality.

several articles suggest that there is no significant impact on these mortality rates, indicating a need for further research. For instance, Rizos et al reported that omega-3 PUFA supplementation did not show an association with mortality.[61] While omega-3 fatty acids may potentially influence health-related factors, additional studies are warranted to understand their effects better.

Regarding HF, studies indicate that administering omega-3 supplements at dosages from 1 to 4 g daily for a duration of 1 to 5 years can reduce mortality rates in patients with HF. However, some studies with similar doses and duration reported no mortality reduction. Further studies are needed to validate these potential mortality benefits for individuals with HF.

4.2. Hospitalization

HF stands as one of the leading causes of hospitalization globally. According to Salah et al, HF was among the top 10 causes of hospital admissions in the United States from 2005 to 2018.[62] A diagnosis of HF has substantial consequences for both patients and the healthcare institutions involved in critical cases. Inadequate patient knowledge, suboptimal medication adherence, noncompliance with physician recommendations, and a lack of thorough professional monitoring can result in rehospitalizations and frequent healthcare visits.[63] HF exhibited the highest 30-day readmission rates at 23.5%.[64] The issue of HF readmission is becoming increasingly significant in both developed and developing countries.[65]

Various initiatives were made to reduce hospitalization and readmission rates among HF patients. Interventions such as promoting medication adherence,[17] encouraging exercise,[66] utilizing ultrafiltration,[67] and administering ferric carboxymaltose[68] have demonstrated the potential to reduce hospitalization and readmission for these patients. Furthermore, nutritional intervention represents an additional key strategy to reduce hospitalization and readmission among HF patients.[69]

As a potential nutritional intervention, omega-3 supplementation can significantly reduce hospitalization and readmission rates. Nodari et al recruited 133 patients with nonischemic cardiomyopathy (NICM) and minimal symptoms on standard therapy and randomized to 2 groups of n-3 PUFA and placebo. Results of the study suggested a slight difference in the hospitalization rate between the n-3 PUFA and placebo groups.[6] The study of Djoussé et al confirmed the positive effects of n-3 PUFA on decreasing hospitalization rates because of HF.[70] It seems clear that n-3 PUFA can be used in cardiology. Most of these studies have supported the proposition that supplementation with n-3 PUFA at a dose of 1 to 4 g/d and at least for over 2 years may reduce the hospitalization rate among patients with HF.

4.3. Myocardial infarction

One of the current challenges lies in finding innovative means to prevent cardiovascular deaths from MI in HF patients, despite the impressive therapeutic advances made over the years.[71] Moreover, studies have shown that n-3 polyunsaturated fatty acids benefit HF patients with MI.[72,73]

Recent studies highlighted the importance of omega-3 in preventing MI in patients with cardiac diseases. Shen et al found that omega-3 supplementation positively reduced the incidence of major adverse cardiovascular events, cardiovascular death, and MI among patients with coronary heart disease.[24]

Omega-3 at a dose of 2 g/d for at least 4 to 12 weeks can positively control events leading to MI in HF patients. However, considering that no positive effect was seen in many articles, it remains controversial and needs more research to evaluate this issue and determine the effective dose.

4.4. Cardiac function

Many studies have been conducted regarding the effectiveness of omega-3 supplementation on the cardiac function of HF patients and the general population. Staffico determined that the lack of daily omega-3 intake can cause an increase in high sensitivity C-reactive protein (hs-CRP), interleukin-2, brain-type natriuretic peptide (BNP), left ventricle (LV) end-diastolic volume and a decrease in left-ventricle ejection fraction (LVEF).[47] The results of the studies also reported that omega-3 has anti-inflammatory and anti-fibrosis effects. A study by Oikonomou showed that short-term treatment with omega-3 PUFAs in patients with stable ischemic HF improved inflammatory and fibrotic status, endothelial function, and LV systolic and diastolic performances.[74] Stefano Ghio conducted a study on 608 patients with chronic HF, showing that n-3 polyunsaturated fatty acids could provide a small but statistically significant advantage in LV function in patients with symptomatic HF.[37] Also, omega-3 has some beneficial physiological effects involving inhibition of thromboxane production, increased production of prostacyclin, increased fibrinolytic activity of plasma, modification of leukotriene and cytokine production to reduce inflammation, decreased platelet-activating factor and platelet-derived growth factor, and oxygen free-radical generation.[75] Chronic inflammation is a characteristic of severe chronic HF (CHF).[76] Inflammatory cytokines have been shown to decline LV function, promote LV remodeling, deteriorate endothelial function,[61] and impair exercise capacity. In addition,[77] the extent of inflammation,[75] endothelial dysfunction, LV remodeling, and functional impairment are predictors of poor prognosis in CHF.[51,78–80] A study by Selvara in 2022 showed that Icosapent Ethyl reduced hs-CRP compared with a placebo, similar to patients without HF.[45]

HF is a significant cause of death worldwide. Circulating biomarkers that reflect the pathophysiological pathways involved in the development and progression of HF may help clinicians in the early diagnosis and management of HF patients. Natriuretic peptides (NPs) are cardioprotective hormones released by cardiomyocytes in response to pressure or volume overload. The role of BNP and N-terminal pro-B-type NP for diagnosis and risk stratification in HF has been widely demonstrated, and these biomarkers have been recognized as emerging tools for screening and disease management.[49]

The effect of an appropriate dose of omega-3 on cardiac function was assessed in patients with HF.[39,40] A randomized 3-arm pilot study evaluated the impact of 1 and 4 g/d omega-3 compared with a placebo in patients with severe CHF. LVEF increased significantly in a dose-dependent manner in the 4 and 1 g/d groups (baseline vs 3 months). Flow-mediated vasodilation rose significantly with high-dose (i.e., 4 g/d omega-3). In the high-dose group, interleukin-6 (IL-6) and high-sensitive tumor necrosis factor alpha (TNF-α) significantly declined. Only a maximum of 4 g/d increased the peak oxygen consumption in patients with maximal exercise effort.[39] A study in Italy determined that LVEF significantly increased at 1, 2, and 3 years in the omega-3 group versus placebo, but other echocardiographic parameters did not change significantly. Also, there was a considerably higher trend of clinical events (all-cause death or hospital admission for cardiovascular reasons) in the group of patients with an LVEF below or equal to the median value than in patients having an LVEF above the median (>30%).[37] Another study in patients more than 60 years old with symptoms of HF showed that omega-3 supplementation had a significant change in inflammatory markers, TNF-α and IL-6, endothelial adhesion molecules, intercellular adhesion molecule 1 (ICAM-1), and N-terminal-pro hormone BNP in HF patients. LVEF demonstrated small but non-significant improvement in the omega-3 PUFA group.[35]

A crossover trial among Caucasian men showed that omega-3 PUFA significantly decreased heart rate (HR) at rest and

improved 1-minute HR recovery after exercise.[32] Also, another study conducted among 25 patients with chronic post-MI systolic HF revealed that omega-3 supplementations in post-MI patients caused partial restoration of several indices of cardiovascular homeostatic control, including baroreceptor control of HR, baroreceptor control of the peripheral vasculature, and HR variability. Another study found that compared to the control group, BNP levels in the omega PUFAs group had a lower value. In addition, end-diastolic and end-systolic LV dimensions and the maximum diameter of the left atrium were decreased in the intervention group. The left atrium ejection fraction was ameliorated in the omega 3-PUFAs intervention group.[43] In line with the effect of omega on important cardiac indicators, a study in Japan showed that in the EPA group, LVEF was improved, and monocyte chemotactic protein-1 (MCP-1) and ADMA levels were reduced. However, in the group without EPA, LVEF was worsened, while MCP-1 and ADMA levels were increased. Multivariate Cox hazard analysis showed that EPA treatment was an independent predictor for cardiac events.[42]

Results also highlighted a significant rise in R-R interval total variance and low-frequency and high-frequency spectral powers. Omega-3 PUFA supplementation significantly potentiates baroreflex function and enhances HR variability in patients with stable congestive HF.[30] A double-blinded, placebo-controlled, 2-arm design study has investigated the effects of omega-3 PUFAs on LV systolic function in CHF and determined that omega-3 supplementation causes a significant rise in LVEF and peak Vo2. Furthermore, there was a significant reduction in the mean of the New York Heart Association functional class and the hospitalization rates in the omega-3 group.[6] Kojuri et al conducted a trial in Shiraz among 70 patients with CHF, and BNP plasma level decreased significantly in the treatment group.[41]

According to the review we conducted, supplementation with omega-3 in more extended period intervention studies at a minimum dose of 1 to 2 g/d and even up to higher doses (8 g/d) for at least 3 to 6 months seems to have some potential beneficial effect on heart function among patients suffering from HF.

4.5. Dysrhythmia

Researchers have been studying omega-3 fatty acids (FAs) and the possibility of their antiarrhythmic properties for decades.[81] Nodari et al studied 44 patients suffering from idiopathic dilated cardiomyopathy (IDC) for 12 months. The patients were randomly assigned to 2 groups (n-3 PUFA or placebo). They received 5 capsules (each capsule containing 1 g of n-3 PUFA) daily for the first month and 1 capsule afterward. Patients with IDC benefited from administering n-3 PUFAs, reducing parameters linked to the arrhythmic risk.[36]

Furthermore, another randomized clinical trial was conducted on 1027 patients with acute MI for 2 years. Patients received 1.8 g of n-3 PUFA daily compared to a placebo group. The results suggested that omega-3 in high doses may increase the risk of bleeding in patients. A secondary analysis of the OMEMI trial also demonstrated a higher risk of new-onset atrial fibrillation (AF) for the cohort with 1.8 g/d of EPA/DHA and corn oil control group for 2 years.[82] According to these data, the effectiveness of omega-3 supplements on arrhythmia is dose-dependent. In the recommended amounts, about (1 g daily), n-3 PUFA supplement can have antiarrhythmic effects; However, higher doses can cause bleeding and worsen the patient condition. Therefore, more studies are required to make a definite recommendation to take omega-3 supplements to improve cardiac arrhythmias.

4.6. Inflammatory factors and plasma lipids

One of the essential pathophysiological factors in CHF is Inflammation,[83] and evidence has shown that increased inflammatory cytokines are associated with complications in cardiac function.[79] Various studies have suggested that n-3 PUFA can reduce inflammatory cytokines.[48] However, most of these studies have been conducted on non-HF patients.[46]

The Nodari et al study on IDC patients revealed that n-3 PUFA administration was associated with lower levels of inflammatory markers TNF-α, IL-1, and IL-6 compared with placebo.[36] Also, treatment with 2 g/d of n-3 PUFA in 76 elderly patients with CHF significantly decreased plasma levels of TNF-α, IL-6, and ICAM-1 after 3 months compared to the placebo. However, plasma hs-CRP and vascular cell adhesion molecule 1 levels did not significantly vary between the 2 groups. In this study, a subgroup analysis determined that compared to nonsmokers, in smokers, plasma hs-CRP levels were significantly higher in both groups. Unlike nonsmokers, n-3 PUFA supplementation significantly reduced plasma hs-CRP levels.[35] In contrast to the previous study, in 138 CHF patients, n-3 PUFA at a dose of 0.9 g/d for 24 weeks did not affect plasma levels of soluble cellular adhesion molecules and hs-CRP compared to placebo. The lack of effect of n-3 PUFA on ICAM-1 in this study is probably due to the lower treatment dose.[38] Furthermore, in 14 patients suffering from advanced HF (New York Heart Association Class III–IV), n-3 fatty acids supplementation at a dose of 8 g/d for 18 weeks resulted in a 59% reduction in TNF-α and a 39% decrease in IL-1 production.[31] Del et al determined that treatment with n-3 fatty acids positively affects levels of platelet- and monocyte-derived microparticles.[34] Morgan et al found that dietary omega-3 fatty acid supplementation was accompanied by increased forearm blood flow response to acetylcholine (ACH), which represents enhanced endothelium-dependent vasodilation in CHF.[33] In a 2022 study by Selvara et al, it was reported that Icosapent Ethyl reduced triglycerides and increased endothelium-dependent vasodilation compared to the placebo, similar to patients without HF.[45]

Although evidence suggests that intake of high-dose omega-3 fatty acids improves many important cardiovascular parameters such as lipids[50] and inflammatory markers,[84] another trial indicated that consumption of 810 mg/d of omega-3 fatty acids for 4 months in HF patients did not significantly improve their EF.[32] In 2 studies by Moertl et al, CHF patients were assigned into 3 groups, including 1 or 4 g/d n-3 PUFA or placebo for 12 weeks. These studies showed that the effects of n3-PUFA consumption on the improvement of inflammation are dose-dependent, and significant beneficial effects on IL-6 were observed with only 4 g/d. On the other hand, no significant trend for the decrease of TNF-α was observed in the high-dose group, and no changes were detected in hs-CRP and MCP-1 levels.[39] A study by Wurm et al reported controversial results by showing that n3-PUFA supplementation diminishes the anti-oxidant function of HDL in nonischemic HF patients.[44] These divisive results demand further extensive studies and information in this regard.

Generally, in the studies we reviewed, inflammatory factors were reduced to > 1 g/d or 2 to 8 g/d n-3 PUFA at least for 3 to 6 months compared to the control groups. Therefore, it is evident that treatment efficacy is associated with dosage. Furthermore, the lack of effect for omega-3 fatty acids on lipid profile after the intervention may be due to the normal baseline lipid levels.

4.7. Other outcomes

There are significant studies about the effectiveness of omega-3 on the QoL of chronic patients.[85–87] Nutritional intervention with omega-3 improves QoL by relieving symptoms and reducing patients' complaints. Omega-3 can also manage and control allergic factors that play an essential role in the symptoms of chronic patients, and this can also be a possible mechanism for improving life quality.[85,87] Jiang showed that omega-3 supplementation resulted in significant changes in the social aspect of QoL among patients with HF.[22] This study also mentioned the

effectiveness of omega-3 supplementation on cognitive depressive symptoms among HF patients. It seems omega-3 supplementation affects depression, but more studies are needed to confirm this hypothesis.

We should highlight the difference between dietary sources of omega-3 fatty acids and dietary supplements. Natural sources of omega-3s include fatty fish (salmon, mackerel, and sardines), flaxseeds, chia seeds, walnuts, and certain plant oils (such as flaxseed oil). These foods are high in omega-3 fatty acids in their natural form. Supplements, on the other hand, are highly processed and frequently contain concentrated forms of omega-3 fatty acids (EPA and DHA), which are typically derived from fish oil or algae. Natural dietary omega-3s are packaged with other nutrients, such as proteins, vitamins, and minerals, which may improve their absorption and utilization in the body. Supplements, mainly concentrated forms, can provide higher doses and potentially higher bioavailability, allowing for more precise intake of specific omega-3 fatty acids. The quality and purity of natural food sources and supplements can differ. Pollutants like mercury, which can be filtered to varying degrees in supplements, may be present in fish used for oil extraction. On the other hand, whole food sources may have lower concentrations of omega-3s but less concern about contaminants.[88,89]

The potential cardiovascular benefits of omega-3 supplementation are attracting the interest of cardiologists and HF specialists. Omega-3 levels may be included in routine screening and risk assessment of HF patients to prevent adverse outcomes. Subsequently, omega-3 supplementation may be prescribed as an adjunct to conventional therapies for patients with low levels of omega-3.

5. Conclusion

Studies have attempted to develop effective heart disease treatments with fewer side effects. It has been suggested that EPA and DHA supplementation can improve patients' conditions by reducing the duration and dose of therapy. n-3 PUFAs also seem to alleviate psychological symptoms in these patients. The supplementation of n-3 PUFAs has improved several clinical outcomes, including hospitalization, MI, stroke, revascularization, cardiac function, arrhythmias, and inflammatory factors. Considering that the included studies were primarily small-scale and limited, the effectiveness of n-3 PUFAs on HF outcomes cannot be definitively confirmed. Thus, large-scale studies are required in this regard. These studies require additional investigation into dosage, duration, and side effects. According to current information, starting n-3 PUFA supplementation in patients with HF appears favorable.

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