SILLDORFF, Julia, FURA, Tomasz, DUDEK, Marcin, ZAUCHA, Radosław, FELIŃSKA, Zuzanna, ISZCZUK, Oliwia, ANCZYK, Stanisław, GAJKIEWICZ, Magdalena and ZAJĄC, Małgorzata. Reducing cardiovascular risk - are omega 3 fatty acids the solution? Quality in Sport. 2024;18:53426. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.18.53426
https://apcz.umk.pl/QS/article/view/53426

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.07.2024. Revised: 22.07.2024. Accepted: 01.08.2024. Published: 08.08.2024.

Reducing cardiovascular risk - are omega 3 fatty acids the solution?

Julia Silldorff, Tomasz Fura, Marcin Dudek, Radosław Zaucha, Magdalena Gajkiewicz, Zuzanna Felińska, Oliwia Iszczuk, Małgorzata Zając, Stanisław Anczyk.

Julia Silldorff
ORCiD:0009-0002-9223-2089
https://orcid.org/0009-0002-9223-2089; juliasilldorff24@gmail.com
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

Tomasz Fura
ORCiD:0009-0008-0947-8058
https://orcid.org/0009-0008-0947-8058; tfura1@gmail.com
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

Marcin Dudek
ORCiD: 0009-0003-6762-0124
https://orcid.org/0009-0003-6762-0124; marcindudek98@gmail.com
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

Radosław Zaucha
ORCiD: 0009-0001-6328-6443
https://orcid.org/0009-0001-6328-6443; radoslaw.zaucha97@gmail.com
Edward Szczeklik Specialist Hospital in Tarnów, Poland

Zuzanna Felińska
ORCiD: 0009-0001-6717-5644
https://orcid.org/0009-0001-6717-5644; zuz1998@gmail.com
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

Oliwia Iszczuk
ORCiD: 0009-0002-0478-9582
https://orcid.org/0009-0002-0478-9582; oliwiaiszczuk@gmail.com
Powiatowy Zespół Zakładów Opieki w Będzinie

Stanisław Anczyk
ORCiD: 0009-0006-8424-2147
https://orcid.org/0009-0006-8424-2147; stanislawanczyk@gmail.com
SKN przy Katedrze i Klinice Dermatologii WNMK w Katowicach

Magdalena Gajkiewicz
ORCiD: 0009-0000-0295-3591
https://orcid.org/0009-0000-0295-3591; gajkiewicz.m@gmail.com
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

Małgorzata Zając
ORCiD: 0009-0003-3870-2382
https://orcid.org/0009-0003-3870-2382; mal.m.zajac@gmail.com
St. Maximilian District Hospital in Oswiecim

Autor do korespondencji:
Julia Silldorff
Wojewódzki Szpital Specjalistyczny nr 5 im.św.Barbary w Sosnowcu, Plac Medyków 1

ABSTRACT

Introduction and objective

Omega-3 fatty acids possess numerous physiological characteristics, including anti-inflammatory, lipid-lowering, antiarrhythmic, and antithrombotic effects. There has been an ongoing discussion about their potential positive effects on human health and the extent of their influence. In this review, we will explore the current understanding of how omega-3 fatty acids impact the development of cardiovascular diseases.

Review methods

A review of publications on the effects of omega 3 fatty acids was conducted using the PubMed platform. The main keywords used in the search were "omega 3 fatty acids" and "cardiovascular diseases". The search included a review of the latest scientific work on the effects of omega 3 fatty acids on the body.

Abbreviated description of the state of knowledge

Omega-3 fatty acids exhibit diverse molecular mechanisms that are beneficial in combating cardiovascular diseases. Reducing serum triglycerides is one of the ways in which omega 3

fatty acids have an advantageous effect on the cardiovascular system. Dietary sources and supplementation offer potential benefits.

Summary

Omega-3 fatty acids, including EPA and DHA, exhibit various molecular mechanisms such as antithrombotic, anti-inflammatory, and lipid-lowering effects, which are crucial in combating CVDs. Dietary sources of omega-3 include both animal and plant products. Supplementing with omega-3 fatty acids, particularly in patients with elevated triglyceride levels, can significantly reduce CVD risk factors and mortality rates. Recommendations suggest consuming 2 servings of fish per week or supplementing with DHA + EPA to support cardiovascular health. Despite some controversies in research findings, omega-3 supplementation remains beneficial. Ongoing research continues to explore the optimal use and efficacy of omega-3 fatty acids in cardiovascular health.

Key words: Omega 3 fatty acids, Cardiovascular diseases, Triglycerides.

Introduction

Cardiovascular diseases is a term including extensive disorders affecting the heart and blood vessels. Many diseases are covered under this term such as coronary heart diseases, stroke and transient ischaemic attack, peripheral arterial disease or aortic diseases [1]. According to the World Health Organization- about 17.9 million people died from CVDs in 2019, which is 32% of all global deaths. The majority, like 85%, were due to heart attack and stroke [2]. Numerous factors play a role in the onset of cardiovascular diseases, such as hypertension, elevated cholesterol, smoking, diabetes, obesity, lack of physical activity, poor dietary habits, excessive alcohol consumption, and a family history of cardiovascular conditions. Making lifestyle changes is essential for preventing cardiovascular diseases. While omega-3 fatty acids show promise in preventing and managing cardiovascular diseases, it's important to note that they should be used as part of a comprehensive approach to heart health, which includes a

balanced diet, regular exercise, maintaining a healthy weight, not smoking, and managing other risk factors such as high blood pressure and diabetes. [3].

Omega-3 FA molecular mechanism

Omega-3 (n-3) fatty acids are a family of polyunsaturated fatty acids (PUFAs) characterized by a double bond at the third carbon atom from the methyl end of the acyl chain. These include, among others: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α-linolenic acid (ALA) [4]. The simplest n-3 fatty acid is α-linolenic acid (ALA; 18:3n-3), which is synthesized from the n-6 fatty acid linoleic acid (LA; 18:2n-6) by the enzyme delta-15 desaturase. While plants possess this enzyme, animals, including humans, do not. That means that ALA is an exogenous fatty acid and needs to be obtained through diet. EPA and DHA are formed from ALA through desaturation as like addition of a double bond between two carbon atoms and elongation, that is, addition of two carbon atoms. The conversion of ALA to EPA, DPA, and DHA in humans is generally inefficient, with particularly low levels of DHA being produced. EPA, DPA, and DHA are found in significant amounts in fish, and these fatty acids are collectively referred to as marine n-3 PUFAs [5].

Omega-3 fatty acids have a number of properties. The antithrombotic effect is a result of inhibition of the synthesis of thromboxane A2, which is a prostaglandin produced by activated platelets that causes platelet activation and aggregation [6]. The anti-inflammatory effect is caused by various mechanisms such as inhibition of chemotaxis that is the movement of the leukocytes towards the place of inflammation, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids [7]. One of the main mechanisms of anti-inflammatory action is the influence on the metabolism of arachidonic acid. An uncontrolled inflammatory reaction underlies the development of atherosclerosis, which plays a role in the pathogenesis of cardiovascular diseases[8]. The lipid-lowering effect is commonly used in treatment of hypertriglyceridemia[9]. It is known that a high concentration of triglycerides is a risk factor of cardiovascular diseases [10]. It seems that the mechanism is based on inhibiting triglycerides resynthesis in the intestinal wall and liver and increasing their degradation in the process of β-oxidation in mitochondria [6,11]. Omega-3 fatty acids are inhibiting the diacylglycerol acetyltransferase in the liver, which is an enzyme that catalyzes the formation of triglycerides from diacylglycerol and acyl-CoA [18]. The recently published EpanoVa for Lowering Very High triglyceridEs II (EVOLVE II) study

confirmed that omega-3 fatty acids are reducing serum TG concentration [12]. Fish oil has a significant effect on lowering blood pressure, most likely by reducing vascular resistance, but it does not reduce cardiac output. The increased production of nitric oxide from omega-3 PUFA intake may boost the expression of endothelial nitric oxide synthase. Various randomized studies have found that omega-3 PUFAs enhance serum markers of endothelial dysfunction, such as E-selectin, VCAM-1, and ICAM-1[32]. Moreover, omega-3 PUFA stabilizes the fluidity of the cell membrane. They become incorporated into cell membranes, where they impact processes like the arachidonic acid cascade, which controls inflammation. Additionally, they help stabilize cell membrane fluidity and can influence the activity of receptors and ion channels. Fish oil, abundant in omega-3 PUFA, exhibits antiarrhythmic properties, potentially preventing sudden death from heart rhythm abnormalities, especially following a heart attack. This protective effect is thought to stem from omega-3 PUFA, particularly docosahexaenoic acid (DHA), inhibiting sodium channels in heart cells [33].

Dietary findings and supplementation

Sources of fatty acids may be products of animal and vegetable origin. Fats in the diet should be supplied primarily from products rich in monounsaturated fatty acids, including PUFA, both from the omega-6 and omega-3 groups[13]. In Western countries, the ratio of omega-6 to omega-3 is, according to various sources, from 10:1 to 25:1 and is unfavorable for health. According to some scientists, the optimal ratio is 4:1 or even 2:1, which is practically unattainable because the diet nowadays is often low in fish and rich in sunflower and rapeseed oil, which are products rich in omega-6 [22,23]. There is insufficient data to indicate the optimal ratio of omega-3 fatty acids to omega-6 fatty acids in the diet. An elevated ratio of omega-6 to omega-3 is linked to a higher risk of chronic diseases such as cardiovascular diseases, cancer, and inflammatory and autoimmune disorders. Adjusting this ratio by boosting omega-3 consumption and lowering omega-6 intake can help reduce these risks and enhance overall health [19].

ALA is found in various plant products (Table 1). Linseed and the oil obtained from it have a very high alpha-linolenic acid content which is the precursor of DHA and EPA[20]. It consists of over 50% ALA and is widely considered to be one of the products rich in this ingredient. It is not recommended to supply the human body only with plant sources of omega-3 FA, because only a portion of ALA is converted to EPA and DHA [14,15]. Animal products contain EPA and DHA in the form of fish oil. The foods richest in these compounds are fish,

especially salmon, herring, mackerel, anchovies, and sardine[16]. Fish themselves do not produce omega-3 fatty acids. The content of this compound in their body comes from the food they eat, i.e. plankton and algae. They are produced in chloroplasts, so their content in meat depends on the individual's diet [17].

Bioavailability is a concept that determines the amount of a substance absorbed and may determine the time in which the substance is absorbed. This is a process that depends on many factors, so the final value of the absorbed product may vary and should be taken into account during supplementation. It has been proven that omega 3 in the form of free fatty acid is more absorbable than that of ethyl esters. This is due to the fact that the absorption of omega 3 ethyl esters is dependent on pancreatic lipase, which carries out hydrolysis. This process depends on the fat in the meal[30]. This is an important advantage for people with hypertriglyceridemia because one of the elements of the treatment of this disease is limiting fats in the diet and high-fat meals are not recommended [31]. In order to maintain health, it is recommended to eat 1 to 2 portions of sea fish a week (according to ECS guidelines 2021). If such a situation is not possible, it is recommended to supplement with DHA + EPA 250 mg/day, which corresponds to the above-mentioned portion of fish [24].

Disease prevention

In patients with elevated triglyceride levels, the recommended dose of omega-3 is 2-3g/day. This intake of fatty acids can reduce triglyceride levels by up to 30%[21,25]. This fact is often used to support therapy with fibrates and statins.

Dyslipidemia is an important factor in atherosclerosis, which directly affects the development of cardiovascular diseases. The risk of cardiovascular diseases increases with triglyceride levels above 150 mg/dl. It is recommended to consider adding an omega-3 PUFA (icosapent ethyl 2 × 2 g/d) to the treatment of triglyceridemia (135–499 mg/dl) in patients at high or very high risk in combination with statins [10,24].

A study was conducted to compare the relationship between the amount of fish consumed and mortality from coronary heart disease. The results show that people eating fish 2-4 servings/week had a much stronger protective effect than people eating fish once a week. Larger amounts of fish, i.e. >5 servings/week, had no protective effect, most likely due to the mercury content in fish, which has a negative impact on human health [26,27]. Furthermore, a linear dose-response analysis showed that each 15 g/day increase in fish consumption reduced coronary heart disease mortality by 6% [26].

In the REDUCE-IT study, patients received highly purified EPA at a dose of 4 g/day. Patients who received the preparation were at risk of cardiovascular diseases, were also under statin therapy and had triglyceridemia. It has been proven that these patients reduced their cardiovascular risk by 25%. We can conclude that the use of omega-3 acids in such people is one of the ways to reduce the risk of cardiovascular diseases [28].

A recent Cochrane review found little or no effect of omega-3 fatty acid preparations on cardiovascular mortality. It has been proven that omega-3 preparations can slightly reduce mortality related to ischemic heart disease. Increased intake of ALA may slightly reduce risk of cardiovascular disease events with little or no difference to mortality. This study concluded that the most beneficial effect in the prevention of cardiovascular risk is through reducing triglycerides by 15% in a dose-dependent way [29].

Research on the efficacy of omega-3 PUFA in patients with implanted defibrillators or atrial fibrillation (AF) has produced inconsistent findings. Omega-3 fatty acids can have beneficial effects on arrhythmias, particularly ventricular arrhythmias, and may reduce the risk of sudden cardiac death. Extensive randomized trials have demonstrated an elevated risk of atrial fibrillation during supplementation with high-dose omega-3 fatty acids. It is crucial to carefully consider the dosage and closely monitor patients, particularly those with existing cardiovascular conditions, to balance the benefits and risks of omega-3 supplementation [34].

Meta-analyses of large prospective cohort studies have indicated that fish oil intake is not associated with an increased risk of hemorrhagic stroke and is inversely associated with the incidence of ischemic stroke when consumed in moderate doses [35]. However, results from prospective intervention studies have been inconsistent. A subanalysis of the JELIS trial using highly purified EPA found no benefit for primary stroke prevention but some benefits for secondary prevention. Consequently, the impact of fish oil and omega-3 PUFA supplements on cardiovascular disease varies widely depending on the study endpoint, which may be influenced by differences in dosage, duration of use, and patient characteristics, including disease severity and concurrent medication use [36].

Conclusions

Omega-3 fatty acids, including EPA and DHA, have multifaceted molecular mechanisms such as antithrombotic, anti-inflammatory, and lipid-lowering effects, all of which are crucial in combating cardiovascular diseases (CVDs). These compounds, sourced from both animal and plant products, have been extensively studied for their potential in preventing and managing

various cardiovascular conditions. It is recommended to consume 2 servings of fish per week. The primary dietary fat sources should be rich in monounsaturated fatty acids, including polyunsaturated fatty acids (PUFAs) from both the omega-6 and omega-3 groups. An increase in the consumption of n-3 fatty acids is associated with a slight decrease, and in some studies even no significant impact, on the incidence of cardiovascular diseases and mortality. Omega-3 preparations appear to provide the greatest benefits in reducing cardiovascular risk by lowering triglyceride levels. In summary, omega-3 fatty acids hold promise as valuable dietary supplements for the prevention and management of cardiovascular diseases, though ongoing research is needed to fully understand their role in specific patient populations and optimize their therapeutic potential.

Author's contribution

Conceptualization: Julia Silldorff

Methodology: Tomasz Fura

Software: Radosław Zaucha

Check: Zuzanna Felińska, Oliwia Iszczuk

Formal Analysis: Magdalena Gajkiewicz, Małgorzata Zając

Investigation: Marcin Dudek

Resources: Stanisław Anczyk

Data curation: Małgorzata Zając

Writing-Rough Preparation: Julia Silldorff

Writing-Review and Editing: Tomasz Fura

Visualization:Magdalena Gajkiewicz, Zuzanna Felińska

Supervision: Radosław Zaucha, Stanisław Anczyk

Project administration: Julia Silldorff

Receiving funding: no funding was received

All authors have read and agreed with the published version of the manuscript.

Disclosures: No disclosures.

Financial support: No financial support was received.

Conflict of interest: The authors declare no conflict of interest.

References

1. Townsend N, Kazakiewicz D, Lucy Wright F, et al. Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol. 2022;19(2):133-143. doi:10.1038/s41569-021-00607-3

2. World Health Organization. Cardiovascular diseases (CVDs). In: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (dostęp 17.05.2024r)

3. Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: A Perspective From Developing Countries. Can J Cardiol. 2021;37(5):733-743. doi:10.1016/j.cjca.2021.02.009

4. "Omega−3 Fatty Acids". Office of Dietary Supplements, US National Institutes of Health. 26 March 2021.

5. Cambiaggi L, Chakravarty A, Noureddine N, Hersberger M. The Role of α-Linolenic Acid and Its Oxylipins in Human Cardiovascular Diseases. Int J Mol Sci. 2023;24(7):6110. Published 2023 Mar 24. doi:10.3390/ijms24076110

6. Ruscica M, Sirtori CR, Carugo S, Calder PC, Corsini A. Omega-3 and cardiovascular prevention - Is this still a choice?. Pharmacol Res. 2022;182:106342. doi:10.1016/j.phrs.2022.106342

7. Shibabaw T. Omega-3 polyunsaturated fatty acids: anti-inflammatory and anti-hypertriglyceridemia mechanisms in cardiovascular disease. Mol Cell Biochem. 2021;476(2):993-1003. doi:10.1007/s11010-020-03965-7

8. Botts SR, Fish JE, Howe KL. Dysfunctional Vascular Endothelium as a Driver of Atherosclerosis: Emerging Insights Into Pathogenesis and Treatment. Front Pharmacol. 2021;12:787541. Published 2021 Dec 22. doi:10.3389/fphar.2021.787541

9. Han SH, Nicholls SJ, Sakuma I, Zhao D, Koh KK. Hypertriglyceridemia and Cardiovascular Diseases: Revisited. Korean Circ J. 2016;46(2):135-144. doi:10.4070/kcj.2016.46.2.135

10. Han SH, Nicholls SJ, Sakuma I, Zhao D, Koh KK. Hypertriglyceridemia and Cardiovascular Diseases: Revisited. Korean Circ J. 2016;46(2):135-144. doi:10.4070/kcj.2016.46.2.135

11. Bornfeldt KE. Triglyceride lowering by omega-3 fatty acids: a mechanism mediated by N-acyl taurines. J Clin Invest. 2021;131(6):e147558. doi:10.1172/JCI147558

12. Stroes ESG, Susekov AV, de Bruin TWA, Kvarnström M, Yang H, Davidson MH. Omega-3 carboxylic acids in patients with severe hypertriglyceridemia: EVOLVE II, a randomized, placebo-controlled trial. J Clin Lipidol. 2018;12(2):321-330. doi:10.1016/j.jacl.2017.10.012

13. Scorletti E, Byrne CD (2013). "Omega−3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease". Annual Review of Nutrition. 33 (1): 231–248. doi:10.1146/annurev-nutr-071812-161230. PMID 23862644

14. Al-Madhagy S, Ashmawy NS, Mamdouh A, Eldahshan OA, Farag MA. A comprehensive review of the health benefits of flaxseed oil in relation to its chemical composition and comparison with other omega-3-rich oils. Eur J Med Res. 2023;28(1):240. Published 2023 Jul 18. doi:10.1186/s40001-023-01203-6

15. Djuricic I, Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. Nutrients. 2021;13(7):2421. Published 2021 Jul 15. doi:10.3390/nu13072421

16. Tomczyk M, Heileson JL, Babiarz M, Calder PC. Athletes Can Benefit from Increased Intake of EPA and DHA-Evaluating the Evidence. Nutrients. 2023;15(23):4925. Published 2023 Nov 26. doi:10.3390/nu15234925

17. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. Circulation. 2017;135(15):e867-e884. doi:10.1161/CIR.0000000000000482

18. Harris WS, Bulchandani D. Why do omega-3 fatty acids lower serum triglycerides?. Curr Opin Lipidol. 2006;17(4):387-393. doi:10.1097/01.mol.0000236363.63840.16

19. Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation. 2009;119(6):902-907. doi:10.1161/CIRCULATIONAHA.108.191627

20. Santos HO, Price JC, Bueno AA. Beyond Fish Oil Supplementation: The Effects of Alternative Plant Sources of Omega-3 Polyunsaturated Fatty Acids upon Lipid Indexes and Cardiometabolic Biomarkers-An Overview. Nutrients. 2020;12(10):3159. Published 2020 Oct 16. doi:10.3390/nu12103159

21. Shen S, Gong C, Jin K, Zhou L, Xiao Y, Ma L. Omega-3 Fatty Acid Supplementation and Coronary Heart Disease Risks: A Meta-Analysis of Randomized Controlled Clinical Trials. Front Nutr. 2022;9:809311. Published 2022 Feb 3. doi:10.3389/fnut.2022.809311

22. Simopoulos AP. An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity. Nutrients. 2016;8(3):128. Published 2016 Mar 2. doi:10.3390/nu8030128

23. Baker EJ, Miles EA, Burdge GC, Yaqoob P, Calder PC. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res. 2016;64:30-56. doi:10.1016/j.plipres.2016.07.002

24. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice (European Heart Journal; 2021 — doi: 10.1093/eurheartj/ehab484).

25. Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation. 2019;140(12):e673-e691. doi:10.1161/CIR.0000000000000709

26. Zheng J, Huang T, Yu Y, Hu X, Yang B, Li D. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. Public Health Nutr. 2012;15(4):725-737. doi:10.1017/S1368980011002254

27. Bradley MA, Barst BD, Basu N. A Review of Mercury Bioavailability in Humans and Fish. Int J Environ Res Public Health. 2017;14(2):169. Published 2017 Feb 10. doi:10.3390/ijerph14020169

28. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

29. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2020;3(3):CD003177. Published 2020 Feb 29. doi:10.1002/14651858.CD003177.pub5

30. Karalis DG. A Review of Clinical Practice Guidelines for the Management of Hypertriglyceridemia: A Focus on High Dose Omega-3 Fatty Acids. Adv Ther. 2017;34(2):300-323. doi:10.1007/s12325-016-0462-y

31. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-2333. doi:10.1161/CIR.0b013e3182160726

32. Robinson JG, Stone NJ. Antiatherosclerotic and antithrombotic effects of omega-3 fatty acids. Am J Cardiol. 2006;98(4A):39i-49i. doi:10.1016/j.amjcard.2005.12.026

33. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits [published correction appears in JAMA. 2007 Feb 14;297(6):590]. JAMA. 2006;296(15):1885-1899. doi:10.1001/jama.296.15.1885

34. Huh JH, Jo SH. Omega-3 fatty acids and atrial fibrillation. Korean J Intern Med. 2023;38(3):282-289. doi:10.3904/kjim.2022.266

35. Xun P, Qin B, Song Y, et al. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. Eur J Clin Nutr. 2012;66(11):1199-1207. doi:10.1038/ejcn.2012.133

36. Tanaka K, Ishikawa Y, Yokoyama M, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial [published correction appears in Stroke. 2008 Sep;39(9): e149]. Stroke. 2008;39(7):2052-2058. doi:10.1161/STROKEAHA.107.509455