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THERAPEUTIC POTENTIAL OF OMEGA-3 FATTY ACIDS IN THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS: A NARRATIVE REVIEW OF THE LITERATURE

POTENCIAL TERAPÊUTICO DOS ÁCIDOS GRAXOS ÔMEGA-3 NA PREVENÇÃO PRIMÁRIA DE EVENTOS CARDIOVASCULARES: REVISÃO NARRATIVA DA LITERATURA

POTENCIAL TERAPÉUTICO DE LOS ÁCIDOS GRASOS OMEGA-3 EN LA PREVENCIÓN PRIMARIA DE EVENTOS CARDIOVASCULARES: UNA REVISIÓN NARRATIVA DE LA LITERATURA

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ABSTRACT

Polyunsaturated fatty acids of the omega-3 family, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been widely investigated for their therapeutic potential in the primary prevention of cardiovascular events. This paper presents a

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comprehensive review of the available evidence on the physiological mechanisms, metabolic effects, and clinical outcomes associated with omega-3 supplementation, with emphasis on recent studies and systematic reviews. These nutrients play an important role in modulating risk factors such as dyslipidemia, subclinical inflammation, and endothelial dysfunction, as well as potentially contributing to the reduction of myocardial infarction and sudden cardiac death. A key finding is the difference in outcomes between the use of high-dose EPA alone, which has shown significant benefits in recent clinical trials, and the combined formulation of EPA+DHA, whose effects on overall cardiovascular mortality remain more uncertain. Although the findings are promising, conflicting results persist, particularly in low-risk populations. In this context, individualized supplementation, combined with rigorous control of modifiable factors, remains a central strategy to reduce the burden of cardiovascular disease.

Keywords: Omega-3. EPA. DHA. Primary Prevention. Polyunsaturated Fatty Acids.

RESUMO
Os ácidos graxos poli-insaturados da família ômega-3, especialmente o ácido eicosapentaenoico (EPA) e o ácido docosahexaenoico (DHA), vêm sendo amplamente investigados por seu potencial terapêutico na prevenção primária de eventos cardiovasculares. Este trabalho apresenta uma revisão abrangente das evidências disponíveis acerca dos mecanismos fisiológicos, dos efeitos metabólicos e dos resultados clínicos associados à suplementação de ômega-3, com destaque para estudos recentes e revisões sistemáticas. Ressalta-se o papel desses nutrientes na modulação de fatores de risco, como dislipidemia, inflamação subclínica e disfunção endotelial, além de sua possível contribuição para a redução de infarto do miocárdio e morte súbita cardíaca. Um aspecto central identificado é a diferença de resultados entre o uso de EPA isolado, que em doses elevadas demonstrou benefícios significativos em ensaios clínicos recentes, e a combinação EPA+DHA, cujos efeitos sobre a mortalidade cardiovascular global permanecem mais incertos. Embora os achados sejam promissores, ainda existem resultados contraditórios, especialmente em populações de baixo risco. Nesse contexto, a individualização da suplementação, aliada ao controle rigoroso de fatores modificáveis, continua sendo elemento central para a redução da carga de doenças cardiovasculares.

Palavras-chave: Ômega-3. EPA. DHA. Prevenção Primária. Ácidos Graxos Poli-Insaturados.

RESUMEN
Los ácidos grasos poliinsaturados de la familia omega-3, especialmente el ácido eicosapentaenoico (EPA) y el ácido docosahexaenoico (DHA), han sido ampliamente investigados por su potencial terapéutico en la prevención primaria de eventos cardiovasculares. Este trabajo presenta una revisión exhaustiva de la evidencia disponible sobre los mecanismos fisiológicos, los efectos metabólicos y los resultados clínicos asociados con la suplementación con omega-3, destacando estudios recientes y revisiones sistemáticas. Se destaca el papel de estos nutrientes en la modulación de factores de riesgo como la dislipidemia, la inflamación subclínica y la disfunción endotelial, así como su posible contribución a la reducción del infarto de miocardio y la muerte súbita cardíaca. Un aspecto clave identificado es la diferencia en los resultados entre el uso de EPA solo, que en dosis altas ha mostrado beneficios significativos en ensayos clínicos recientes, y la combinación de EPA y DHA, cuyos efectos sobre la mortalidad cardiovascular general siguen siendo más

inciertos. Si bien los hallazgos son prometedores, aún existen resultados contradictorios, especialmente en poblaciones de bajo riesgo. En este contexto, la suplementación individualizada, combinada con un control riguroso de los factores modificables, sigue siendo un elemento clave para reducir la carga de enfermedad cardiovascular.

Palabras clave: Omega-3. EPA. DHA. Prevención Primaria. Ácidos Grasos Poliinsaturados.

1 INTRODUCTION

Cardiovascular diseases (CVD) have been the leading cause of morbidity and mortality in the world for decades, representing an ongoing challenge to global public health. Estimates from the World Health Organization (WHO, 2023) indicate that about 17.9 million people die annually as a result of these conditions, which corresponds to approximately 32% of all global deaths. In this context, primary prevention strategies have gained prominence, especially those aimed at modulating modifiable risk factors, such as diet, physical activity, and metabolic control. Among the nutrients investigated, polyunsaturated fatty acids of the omega-3 family, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), emerge as promising candidates to reduce the incidence of cardiovascular events.

Scientific interest in the cardioprotective effects of omega-3 fatty acids has historical roots. Pioneering studies conducted with Greenland Inuit populations in the 1970s and 1980s observed low rates of coronary artery disease among individuals with a diet rich in marine fish (Bang; Dyerberg, 1972; Dyerberg et al., 1978). This initial evidence has stimulated the development of clinical trials and mechanistic investigations that have broadened the understanding of the effects of these essential lipids on cardiovascular physiology. Just as the concept of atherosclerosis has evolved to be understood as a chronic inflammatory process (Ross, 1999), the role of omega-3s has been investigated not only in relation to lipid reduction, but also as modulators of inflammatory and hemodynamic pathways.

In recent decades, the scientific literature has shown that omega-3 fatty acids exert multiple beneficial effects, including lowering serum triglycerides, improving endothelial function, increasing arterial elasticity, and modulating the inflammatory response (Innes; Calder, 2020). Randomized clinical trials, such as GISSI-Prevenzione (1999), demonstrated that supplementation with EPA and DHA was associated with a significant reduction in mortality from cardiovascular causes and sudden cardiac death. Subsequently, more recent studies, such as REDUCE-IT (Bhatt et al., 2019), reinforced the efficacy of EPA alone in reducing major cardiovascular events, inaugurating a new phase in the scientific debate on the differential efficacy between EPA and the EPA+DHA combination.

However, the results are not unanimous. High-quality systematic reviews, such as the one published by Cochrane (Abdelhamid et al., 2020), have found little or no effect of omega-3s on overall cardiovascular mortality, although they recognize a positive impact on triglyceride reduction and some intermediate outcomes. This ambiguity highlights the complexity of cardiovascular pathophysiology and the need to interpret the findings in the

light of population characteristics, the type of supplement used, the doses administered, and the presence or absence of previous risk factors.

In the Brazilian epidemiological scenario, the relevance of the topic is even more evident. Data from the Global Burden of Disease (Ribeiro et al., 2019) show that, despite advances in access to pharmacological therapies and percutaneous interventions, cardiovascular diseases remain the leading cause of death in the country, with a strong socioeconomic impact. In this context, low-cost and far-reaching nutritional interventions, such as the incorporation of omega-3 sources into the diet, may represent relevant public health strategies for primary prevention, especially in high-risk populations.

Another important aspect involves the pathophysiological mechanisms modulated by omega-3s. The formation of resolvins and proteins, bioactive derivatives of EPA and DHA metabolism, has been associated with resolution of inflammation and stabilization of atherosclerotic plaque (Calder, 2017). In addition, there is evidence that these fatty acids act in the regulation of heart rate, in the reduction of platelet aggregation, and in the improvement of autonomic function, factors that, together, contribute to a lower predisposition to fatal arrhythmias and acute coronary events.

It is important to note, however, that omega-3 supplementation should not be considered an isolated solution. Primary prevention of cardiovascular events requires a multifactorial approach, which includes smoking cessation, regular physical activity, blood pressure and blood glucose control, and the adoption of cardioprotective dietary patterns, such as the Mediterranean diet. In this scenario, omega-3 fatty acids are adjuvants of great scientific interest, but whose effectiveness should be continuously reevaluated in the face of emerging evidence.

Thus, the present study aims to review the current clinical evidence on the therapeutic potential of omega-3 fatty acids in the primary prevention of cardiovascular events, with emphasis on pathophysiological mechanisms, scientific controversies, and perspectives for application in public health.

2 METHODOLOGY

The present work is characterized as an exploratory narrative literature review, whose main objective is to gather, analyze and discuss the current clinical evidence related to the therapeutic potential of omega-3 fatty acids in the primary prevention of cardiovascular events. The choice for this type of methodology stems from the wide scientific production

available, which includes clinical trials, systematic reviews, meta-analyses, and observational studies, which need to be critically integrated to offer the reader a comprehensive and up-to-date view.

According to Innes and Calder (2020), understanding the effects of omega-3 fatty acids requires not only the analysis of clinical results, but also the investigation of pathophysiological mechanisms, including their anti-inflammatory action, triglyceride reduction, and atherosclerotic plaque stabilization. In this sense, the literature review allows the construction of a panorama that includes from the first epidemiological observations in populations with high fish intake (Bang; Dyerberg, 1972; Dyerberg et al., 1978) to contemporary meta-analyses published in high-impact journals (Abdelhamid et al., 2020; Dinu et al., 2024).

2.1 TYPE OF STUDY AND JUSTIFICATION

The study was developed in the form of a narrative and descriptive review. This choice is justified by the comprehensive nature of the topic and the need to integrate different perspectives, from classic studies to recent trials, such as REDUCE-IT (Bhatt et al., 2019), which specifically investigated the role of the EPA alone. Unlike systematic reviews, which follow strict protocols such as PRISMA, narrative review allows for greater flexibility in the integration of multiple sources, including clinical trials, systematic reviews, guidelines from medical societies, and epidemiological data.

According to Calder (2017), understanding the physiological effects of omega-3 fatty acids requires an integrative approach, in which metabolic, inflammatory, and epidemiological aspects are discussed interdependently. Thus, the option for the narrative review is consistent with the central objective of this study: to critically analyze the body of evidence about the efficacy and limitations of omega-3 supplementation in cardiovascular prevention.

2.2 SEARCH STRATEGY AND SELECTION OF SOURCES

The bibliographic survey was conducted between March and June 2025, by consulting databases of international relevance, such as PubMed, Scopus, Web of Science, SciELO, and LILACS. In addition, reference books in the areas of nutrition and physiology, as well as international guidelines for cardiology and nutrition, were included in order to ensure the comprehensiveness and timeliness of the information analyzed.

The descriptors used (in Portuguese and English) were:

- "omega-3 fatty acids";
- "EPA" / "eicosapentaenoic acid";
- "DHA" / "docosahexaenoic acid";
- "primary prevention";
- "cardiovascular events";
- "myocardial infarction";
- "supplementation".

As inclusion criteria, articles, guidelines and books were selected that:

- directly address the topic of omega-3s and cardiovascular prevention;
- presented relevant clinical, pathophysiological or epidemiological data;
- were published in Portuguese, English, French or Spanish;
- were indexed in journals of recognized scientific quality.

Opinion articles without scientific support, duplicate studies, and studies with low clinical relevance to the theme were excluded.

2.3 SOURCES USED

Among the classic studies, the investigations of Bang and Dyerberg (1972) on Inuit populations stand out, as well as the first large-scale clinical trials, such as GISSI-Prevenzione (1999). In the field of recent publications, Cochrane meta-analyses (Abdelhamid et al., 2020) and reviews in high-impact journals were considered, such as the one published by Innes and Calder (2020) in the *International Journal of Molecular Sciences*. Also included were highly relevant clinical trials, such as REDUCE-IT (Bhatt et al., 2019), in addition to the meta-analysis by Dinu et al. (2024), which investigated the differential effects of EPA alone compared to the EPA+DHA combination.

2.4 ANALYSIS PROCEDURE

The analysis process followed three main steps:

The process of analyzing the sources followed three complementary stages. The **exploratory reading** consisted of the initial identification of the main concepts and evidence present in each work. Then, selective **reading** allowed for a deeper look at the most relevant materials, with an emphasis on randomized clinical trials, systematic reviews, and international guidelines. Finally, **integrative reading** enabled the critical organization of the

contents into thematic axes, including: pathophysiological mechanisms (Calder, 2017), classic clinical trials (GISSI-Prevenzione, 1999), systematic reviews (Abdelhamid et al., 2020) and recent studies on APD alone (Bhatt et al., 2019; Dinu et al., 2024).

2.5 METHODOLOGICAL LIMITATIONS

As it is a narrative review, this study did not follow strict protocols characteristic of systematic reviews, which confers a greater degree of subjectivity to the selection and analysis of the included works. To mitigate this limitation, we sought to contemplate a wide range of references, both historical and contemporary, ensuring diversity of perspectives and consistency in the discussion. Another relevant limitation refers to the dynamic nature of the area investigated: new clinical trials and reviews are constantly published, which may require periodic updates of the present study in order to maintain its validity and topicality.

2.6 RELEVANCE OF THE METHODOLOGY

The option for the narrative review proved to be pertinent because it allowed the recovery of the historical and scientific trajectory of knowledge about omega-3 fatty acids, ranging from the first epidemiological observations to the most recent clinical evidence. This format also enables a broader understanding of the multifactorial complexity of cardiovascular prevention, which involves the interaction between diet, lipid metabolism, inflammatory processes, and clinical risk (Innes; Calder, 2020). The integration of classical and contemporary sources strengthens the consistency of the analysis and contributes to the construction of a critical and comprehensive overview of the role of omega-3 fatty acids in cardiovascular health.

3 RESULTS

3.1 PATHOPHYSIOLOGICAL AND METABOLIC MECHANISMS

The cardioprotective effects of omega-3 fatty acids are closely associated with modulation of lipid metabolism and inflammatory response. Pioneering studies conducted in Inuit populations have identified low rates of coronary artery disease correlated with high consumption of fish rich in EPA and DHA (Bang; Dyerberg, 1972; Dyerberg et al., 1978). Subsequently, laboratory research confirmed that these compounds reduce hepatic production of VLDL, favor fatty acid oxidation, and promote the reduction of serum triglyceride levels by up to 30% in certain contexts (Innes; Calder, 2020). In addition, bioactive

derivatives, such as resolvins and protectins, play a crucial role in resolving inflammation and stabilizing atherosclerotic plaques (Calder, 2017).

Another prominent mechanism refers to the influence on endothelial and autonomic function. Evidence shows that omega-3s potentiate nitric oxide-dependent vasodilation, reduce platelet aggregation, and modulate heart rate, which contributes to a lower predisposition to malignant arrhythmias (Innes; Calder, 2020). Thus, the pathophysiological impact of omega-3s transcends the simple control of the lipid profile, extending to inflammatory, endothelial and electrophysiological dimensions.

3.2 CLINICAL TRIALS AND REDEFINITIONS OF EVIDENCE

The clinical literature on omega-3 fatty acids has gone through different phases regarding the recognition of their effectiveness. The **GISSI-Prevenzione trial (1999)** represented an initial milestone in demonstrating a reduction in cardiovascular mortality and the incidence of sudden death in patients supplemented with EPA and DHA after myocardial infarction. Years later, the **REDUCE-IT study (Bhatt et al., 2019)** reconfigured the debate by showing that EPA alone, administered in high doses, was able to significantly reduce the occurrence of major cardiovascular events, including acute myocardial infarction and stroke.

On the other hand, high-quality systematic reviews, such as the **Cochrane one (Abdelhamid et al., 2020),** have indicated that combined EPA and DHA supplementation has little or no effect on overall cardiovascular mortality. This contrast reinforces the need to interpret the results in the light of critical variables, such as the formulation used (EPA alone vs. EPA+DHA), the dose administered, and the risk profile of the population investigated.

3.3 EPIDEMIOLOGY AND CLINICAL IMPACT

From a population point of view, supplementation or consumption of omega-3 fatty acids has been associated with a lower incidence of coronary events in high-risk groups, although the benefits in healthy individuals are more discreet. The meta-analysis by **Dinu et al. (2024),** involving approximately 149 thousand participants, showed that APE alone significantly reduced both cardiovascular deaths (RR ≈ 0.82) and non-fatal infarctions (RR ≈ 0.72). In the Brazilian context, marked by the high burden of cardiovascular diseases described by **Ribeiro et al. (2019),** the implementation of primary prevention strategies that include encouraging the consumption of foods rich in omega-3 may represent a relevant public health measure.

3.4 SUPPLEMENTATION STRATEGIES AND RECOMMENDATIONS

Current recommendations from international societies suggest a minimum intake of **250 mg/day of EPA+DHA** for the maintenance of cardiovascular health (WHO, 2023), although additional benefits may require higher doses, especially in patients with hypertriglyceridemia. Clinical trials such as **REDUCE-IT** support the use of **4 g/day of EPA** in high-risk populations (Bhatt et al., 2019). However, indiscriminate supplementation is not indicated, since adverse effects, such as a higher risk of atrial fibrillation and bleeding, have been reported in some studies (Innes; Calder, 2020).

Another relevant aspect concerns the differences between dietary sources and pharmacological supplements. While diets rich in marine fish are consistently associated with reduced cardiovascular mortality, the results regarding concentrated fish oil capsules are more heterogeneous. Such a discrepancy suggests that the dietary context, the presence of natural antioxidants, and the interaction with other nutrients may enhance the effects of omega-3s, factors that have not yet been explored in clinical trials (Calder, 2017).

In addition, studies on adherence show that long-term supplementation has higher dropout rates compared to dietary interventions. In this sense, public health strategies that encourage cardioprotective dietary patterns, such as the **Mediterranean diet**, tend to produce more sustainable results than the exclusive dependence on omega-3 capsules (Innes; Calder, 2020).

3.5 HISTORICAL AND SCIENTIFIC INTEGRATION

The trajectory of knowledge about omega-3 fatty acids is marked by important historical milestones. The initial observations of **Bang and Dyerberg (1972),** when investigating populations with diets rich in fish, supported the concept of essential fatty acids as cardioprotective agents. In the following decades, this understanding was expanded, culminating in systematic reviews, such as those by **Cochrane (Abdelhamid et al., 2020**), which introduced counterpoints by showing less consistent results in low-risk populations. More recently, studies involving **EPA alone** have revived scientific interest, highlighting the relevance of differentiating the effects between different omega-3 formulations and reinforcing the need for specific interpretations according to the clinical context.

3.6 SUMMARY OF RESULTS

Based on the analysis of the literature, the main results can be summarized in four axes:

1. Pathophysiological advances: Omega-3s modulate lipids, inflammation, and endothelial function, favoring atherosclerotic plaque stability (CALDER, 2017; INNES; CALDER, 2020).
2. Clinical evidence: Trials such as *GISSI-Prevenzione* and *REDUCE-IT* have demonstrated a significant reduction in cardiovascular events, especially with EPA alone (BHATT et al., 2019).
3. Population impact: The benefits are more evident in high-risk individuals, while the results in healthy populations remain controversial (ABDELHAMID et al., 2020; DINU et al., 2024).
4. Practical recommendations: Supplementation should be individualized, with doses adjusted to the clinical profile and associated with comprehensive primary prevention strategies (WHO, 2023).

Thus, the results reinforce that omega-3 fatty acids play a potentially relevant role in the primary prevention of cardiovascular events, although the magnitude of the benefit depends on the type of fatty acid, the dose, and the risk profile of the population studied.

4 DISCUSSION

The therapeutic potential of omega-3 fatty acids in the primary prevention of cardiovascular events is one of the most debated topics in contemporary nutritional cardiology, especially due to the heterogeneity of the available clinical results. Although the association between diets rich in fish and lower incidence of coronary heart disease has been observed since classical studies in Inuit populations (Bang; Dyerberg, 1972; Dyerberg et al., 1978), controversies persist regarding the magnitude of the benefit of supplementation, particularly when compared to already consolidated pharmacological strategies to reduce cardiovascular risk.

From a historical point of view, pioneering clinical trials, such as **GISSI-Prevenzione (1999),** reinforced the hypothesis that EPA and DHA could reduce cardiovascular mortality and the incidence of sudden death, establishing a paradigm of efficacy. However, recent systematic reviews, such as the **Cochrane review (Abdelhamid et al., 2020),** have shown

little or no effect on overall cardiovascular mortality, highlighting the complexity of interpreting the findings. This divergence reinforces the need to distinguish the effects of specific formulations (EPA alone versus EPA+DHA), in addition to considering variables such as dose, duration of use, and risk profile of the population studied.

The pathophysiology of atherosclerosis provides a solid basis for investigating the role of omega-3s. Unlike the traditional conception of atherosclerosis as a simple lipid accumulation, Ross (1999) consolidated its characterization as a chronic inflammatory process. In this context, EPA and DHA have relevant anti-inflammatory effects, modulating cytokines, stabilizing atherosclerotic plaques, and favoring the resolution of inflammation through the production of resolvins and protectins (Calder, 2017). This biological plausibility supports clinical findings that associate omega-3 consumption with a lower incidence of fatal arrhythmias and non-fatal infarctions, although the results remain heterogeneous.

International guidelines reflect these nuances. The **American Heart Association (AHA)** and the **European Society of Cardiology (ESC)** recognize the benefits of regular fish intake and moderate consumption of EPA+DHA for the maintenance of cardiovascular health, although they emphasize that the greatest benefits in primary prevention are observed in high-risk individuals (Innes; Calder, 2020). At the same time, recent trials, such as **REDUCE-IT (Bhatt et al., 2019),** demonstrated that the use of high-dose EPA alone promoted a significant reduction in infarction and cardiovascular death, reigniting the debate about the possible superiority of specific formulations.

Still, omega-3 supplementation is not without risks. Studies have shown an increase in the incidence of atrial fibrillation in individuals supplemented with EPA alone, as well as a higher risk of bleeding in predisposed populations (Dinu et al., 2024). These findings reinforce the need for individualization of conduct, considering not only the potential benefits, but also the safety implications.

Another crucial point is the distinction between primary and secondary prevention. In patients with established cardiovascular disease, omega-3 supplementation has more consistent results in terms of reduced mortality and recurrence of events. In primary prevention, the effects tend to be more modest and strongly dependent on metabolic risk factors, such as hypertriglyceridemia (Abdelhamid et al., 2020). This differentiation supports the importance of clinical risk stratification in decision-making.

The epidemiological analysis reinforces the relevance of the topic in developing countries, such as Brazil, where cardiovascular mortality remains high (Ribeiro et al., 2019).

In this scenario, encouraging the consumption of omega-3-rich foods, such as deep-sea fish, seeds, and oilseeds, may represent a low-cost public health strategy. However, inequalities in access to these foods limit their applicability on a large scale, demanding nutritional policies that value more accessible regional alternatives.

Another relevant aspect refers to the interaction with pharmacological therapies. In patients already on statins, the additional benefit of omega-3s on clinical outcomes remains controversial. However, the meta-analysis by **Dinu et al. (2024)** suggests that EPA alone maintains efficacy even in individuals under lipid-lowering therapy, reinforcing its usefulness in specific subgroups.

Differences between food sources and supplements are also worth mentioning. While regular fish consumption demonstrates a consistent association with lower cardiovascular mortality, the results of industrial fish oil supplements are more variable (Innes; Calder, 2020). This contrast suggests that the food matrix, the presence of natural antioxidants, and the interaction with other nutrients can enhance the protective effects, a gap that has not yet been explored in clinical trials.

Another challenge is population adherence. Public health evidence indicates that long-term supplementation with omega-3 capsules has a lower adherence rate compared to interventions based on dietary patterns (WHO, 2023). In this sense, sustainable preventive strategies seem to depend more on the promotion of cardioprotective diets, such as the Mediterranean diet, than on supplementation alone.

Finally, the advancement of personalized medicine and nutritional genomics introduces new perspectives. Individual genetic variations can modulate the response to omega-3 supplementation, influencing metabolic and inflammatory outcomes (Calder, 2017). This emerging field tends to redefine in the medium term which population subgroups will benefit more significantly, guiding increasingly precise conducts.

In summary, the role of omega-3s in the primary prevention of cardiovascular events should be analyzed under multiple dimensions, including biological plausibility, heterogeneous results from clinical trials, potential risks, and public health implications. Despite the advances, gaps remain regarding the optimal dose, the choice between EPA and DHA, and the selection of patients who would benefit most from supplementation. Thus, future research should prioritize comparative multicenter trials, involving different formulations and diverse populations, in order to consolidate omega-3s as a safe and effective tool in preventive cardiology.

5 CONCLUSION

Omega-3 fatty acids are one of the main nutritional strategies under investigation for the primary prevention of cardiovascular events, both due to their pathophysiological plausibility and wide food availability. Unlike classic cardiology drugs, whose impact is already well established, omega-3s have heterogeneous clinical results, requiring careful interpretation of the evidence and individualized application (Innes; Calder, 2020; Abdelhamid et al., 2020).

From the pathophysiological perspective, it was evidenced throughout this study that the cardioprotective potential of omega-3 is closely associated with the modulation of atherosclerotic inflammation and the reduction of serum triglycerides, phenomena already described by Ross (1999) and widely deepened in subsequent decades. Atherosclerotic plaque stabilization, improved endothelial function, and antiarrhythmic effects constitute the core of the mechanisms by which EPA and DHA contribute to a lower risk of coronary events, distinguishing them from other less specific dietary interventions (Calder, 2017; Innes; Calder, 2020).

Advances in clinical trials have been instrumental in redefining the role of omega-3s in cardiovascular prevention. While initial studies, such as **GISSI-Prevenzione (1999),** pointed to significant reductions in mortality, later systematic reviews, such as the **Cochrane one (Abdelhamid et al., 2020),** brought more modest results in primary prevention, highlighting the need for risk stratification to assess its real effectiveness. In this sense, **REDUCE-IT (Bhatt et al., 2019)** represented a turning point, by demonstrating that EPA alone, at high doses, significantly reduced major cardiovascular events, establishing a new paradigm for supplementation.

In the field of practical recommendations, current evidence suggests that regular consumption of fish or moderate EPA+DHA supplementation bring overall benefits to cardiovascular health, while pharmacological doses of EPA alone seem more appropriate for individuals at high risk, such as those with atherogenic dyslipidemia or hypertriglyceridemia (Dinu et al., 2024; WHO, 2023). This differentiation is crucial to guide clinical conduct and avoid indiscriminate supplementation, which can lead to risks such as atrial fibrillation and bleeding episodes.

Despite the advances, the global reduction in cardiovascular mortality associated with omega-3 is still a subject of debate, due to the heterogeneity of the findings. This scenario reinforces the need for new multicenter trials that investigate optimal doses, direct

comparisons between EPA and DHA, and applicability in different populations, including in developing countries such as Brazil, where cardiovascular mortality remains high (Ribeiro et al., 2019).

In addition, it is essential to understand omega-3s within a broader context of primary prevention, which encompasses the strict control of traditional risk factors, such as hypertension, diabetes, dyslipidemia, smoking, and sedentary lifestyle. Thus, encouraging healthy lifestyle habits, associated with the balanced consumption of omega-3 food sources, is one of the most promising strategies to reduce the global burden of cardiovascular diseases.

In summary, the preventive approach with omega-3 has evolved significantly in recent decades, accompanied by advances in pathophysiological understanding, greater clarity regarding efficacy in different clinical scenarios, and progressively more individualized recommendations. However, relevant challenges remain, such as defining the most effective formulation, determining safe doses, and ensuring equity in access to omega-3-rich foods. The future points to an increasingly precise cardiovascular medicine, in which these essential fatty acids can play a central role as allies in promoting health and reducing cardiovascular mortality.

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