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EFFICACY OF HIGH-DOSE OMEGA-3 FATTY ACIDS IN MANAGING HYPERTRIGLYCERIDEMIA AND REDUCING CARDIOVASCULAR RISK: A SYSTEMATIC REVIEW OF HISTORICAL AND CONTEMPORARY EVIDENCE

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ABSTRACT
Hypertriglyceridemia (HTG) is a critical modifiable risk factor for atherosclerotic cardiovascular disease. To evaluate the efficacy of high-dose marine lipids, a structured systematic review was executed. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, electronic database searches across PubMed, the Cochrane Library, and Google Scholar yielded an initial 1,800 records. After removing 400 duplicates, 1,400 unique records were screened by title and abstract, resulting in the exclusion of 120 papers. Out of 1,280 full-text articles rigorously assessed for eligibility, 1,250 papers were excluded due to non-randomized controlled trial designs or insufficient dosing durations under six weeks, leaving a final selection of 30 distinct studies. Prescription omega-3 interventions consistently lowered fasting triglyceride parameters. Highly purified eicosapentaenoic acid (EPA) monotherapy significantly reduced major adverse cardiovascular events (MACE), whereas combined EPA and docosahexaenoic acid (DHA) formulations demonstrated inconsistent clinical efficacy. In patients with concurrent type 2 diabetes, therapeutic omega-3 regimens generated robust triglyceride reductions alongside strong anti-inflammatory responses, though high-dose administrations were associated with a modest increase in the relative risk of incident atrial fibrillation. In conclusion, high-dose prescription omega-3 fatty acids are a potent tool for mitigating HTG, with purified EPA providing more reliable reductions in MACE compared to mixed formulations.

KEYWORDS: Omega-3 Fatty Acids; Hypertriglyceridemia; Cardiovascular Disease; Eicosapentaenoic Acid; Icosapent Ethyl; Type 2 Diabetes

INTRODUCTION AND BACKGROUND

Early clinical interest in marine lipids arose during the 1970s following epidemiological investigations of Greenland Inuit populations [1]. Despite consuming a high-fat diet that comprised approximately 40% of their daily caloric intake, these populations exhibited remarkably low mortality rates from cardiovascular events [1]. This cardioprotection was subsequently linked to a high dietary consumption of marine-derived omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [1,2]. These historical observations catalyzed decades of intensive clinical research into the therapeutic role of omega-3 fatty acids for managing hypertriglyceridemia (HTG) [3]. Defined as a fasting serum triglyceride (TG) level at or above 150 mg/dL, HTG is a critical, modifiable risk factor for atherosclerotic cardiovascular disease (CVD) [3]. Mechanistically, elevated triglycerides drive atherogenesis by stimulating the hepatic production and accumulation of triglyceride-rich lipoprotein particles, including very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL), while simultaneously depressing high-density lipoprotein cholesterol (HDL-C) concentrations [3]. Omega-3 fatty acids mitigate this profile primarily by suppressing hepatic VLDL synthesis via the down-regulation of crucial lipogenic enzymes, such as diacylglycerol acyltransferase, alongside a concomitant upregulation of peroxisomal fatty acid beta-oxidation and lipoprotein lipase (LPL) activity [4,5]. To target severe presentations of this metabolic disorder (TG >500 mg/dL), regulatory bodies approved therapeutic options like Lovaza, a specialized omega-3 acid ethyl ester formulation yielding approximately 465 mg of EPA and 375 mg of DHA per gram [6]. Administered at prescription dosages of 3 to 4 g/day, this agent effectively reduces serum TG concentrations by 25% to 50% [6,7].

The clinical landscape for managing this condition shifted further with the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) guidelines [8]. This consensus statement codified normal fasting TG boundaries below 150 mg/dL and established non-HDL cholesterol (non-HDL-C) as a key, secondary therapeutic metric for individuals presenting with elevated baseline triglycerides [8].

Hypertriglyceridemia represents a highly pervasive metabolic challenge, impacting approximately 33% of the adult population in the United States and presenting in 50% to 70% of individuals diagnosed with type 2 diabetes (T2D)

[9,10,11]. This lipid disorder accelerates arterial plaque formation through a distinct shift characterized by elevated triglyceride-rich remnant fractions and depressed circulating HDL-C levels [3].
Prescription-grade omega-3 fatty acid interventions effectively counter this atherogenic profile, yielding substantial 25% to 50% reductions in serum TG parameters when administered at therapeutic ranges of 2 to 4 g/day [6,12,13]. Beyond simple lipid-lowering capabilities, emerging data highlights profound metabolic advantages for patients with comorbid T2D and established high-risk cardiovascular profiles [13].
To clarify these evolving therapeutic landscapes, this systematic review provides a comprehensive synthesis contrasting historical clinical data (1995-2014) against contemporary large-scale trial evidence (2015-2025). This analysis focuses specifically on defining precise mechanisms of action, clinical efficacy curves, and targeted clinical outcomes within diabetic cohorts.

Mechanisms of HTG Atherogenicity
The atherogenic potential of HTG is driven by specific structural alterations in circulating lipid subfractions. Elevated serum triglycerides induce a profound increase in apolipoprotein B-100 (apoB-100) and elevate non-HDL-C concentrations through an expansion of VLDL, IDL, and low-density lipoprotein (LDL) particle counts [14,15]. Within this environment, a high-TG state drives the remodeling of LDL into small, highly dense LDL particles [15]. These compressed, small dense LDL subfractions penetrate the arterial endothelial intima with greater ease, leading to accelerated subendothelial retention, oxidation, and subsequent macrophage-driven foam cell formation [15].
Furthermore, elevated expressions of apolipoprotein C-III (apoC-III) act as a potent inhibitor of endothelial lipoprotein lipase (LPL) [16]. This systemic inhibition impairs the vascular clearance of triglyceride-rich lipoprotein remnants, prolonging their circulation times and exacerbating vascular endothelial inflammation [16]. Reflecting these physiological realities, recent clinical datasets have increasingly positioned apoB-100 and non-HDL-C as more precise, reliable predictors of net cardiovascular risk than traditional LDL-C metrics alone [17,18]. This predictive superiority is particularly pronounced in diabetic populations, where a high prevalence of small dense LDL frequently masks the true extent of atherogenic risk when using standard lipid panels [17].

Causes of HTG
The etiology of hypertriglyceridemia is divided into primary genetic mutations and secondary acquired environmental or metabolic influences. Primary genetic abnormalities including familial hypertriglyceridemia and Fredrickson Type IV phenotypes account for roughly 45% of clinical presentations [19]. Conversely, the remaining majority of cases stem from secondary factors [20]. These acquired causes prominently encompass chronic kidney disease, uncontrolled type 2 diabetes, obesity, physical inactivity, high-carbohydrate dietary patterns exceeding 60% of total caloric intake, and specific pharmacological regimens such as systemic corticosteroids or exogenous estrogens [20].
In the specific context of T2D, chronic insulin resistance impairs normal metabolic pathways, causing an uninhibited influx of free fatty acids to the liver [11]. This flux upregulates hepatic VLDL synthesis and secretion, resulting in profound secondary hypertriglyceridemia [11]. Contemporary epidemiological data confirms that overall HTG prevalence rates remain hovering around 33% across developed nations, a reality increasingly fueled by rising international rates of obesity and type 2 diabetes [10].

Categories of Serum Triglycerides
According to the foundational criteria established by the ATP III guidelines, fasting serum triglyceride concentrations are stratified into distinct clinical tiers: normal levels are maintained strictly below 150 mg/dL, borderline-high parameters range from 150 to 199 mg/dL, high levels span 200 to 499 mg/dL, and very high presentations are defined at or above 500 mg/dL [8]. Presentations within the very high tier drastically escalate an individual's absolute risk for developing acute pancreatitis, a medical emergency requiring rapid, targeted pharmacological strategies to lower systemic lipids [7]. Furthermore, current clinical guidelines emphasize non-HDL-C as a critical, mandatory secondary target for lipid-lowering therapies when managing elevated TG levels, particularly in diabetic populations exhibiting mixed dyslipidemia [21].

Biochemistry of Omega-3 Fatty Acids
The primary, biologically active marine omega-3 fatty acids specifically EPA and DHA are sourced predominantly from fatty marine teleosts such as salmon. Unlike plant-derived alpha-linolenic acid (ALA), which exhibits an extremely inefficient metabolic conversion rate of less than 1% to EPA or DHA within humans, direct dietary or pharmacological ingestion of EPA and DHA is mandatory to achieve therapeutic concentrations [22]. Within clinical practice, prescription-grade ethyl ester mixtures are utilized to treat severe hypertriglyceridemia equal to or exceeding 500 mg/dL, whereas purified icosapent ethyl formulations are deployed specifically to attenuate residual cardiovascular risk [12,13].

Omega-3 TG-Lowering Mechanisms
Omega-3 polyunsaturated fatty acids exert their triglyceride-lowering effects through three distinct and highly coordinated physiological pathways. First, they actively inhibit hepatic triglyceride synthesis and subsequent VLDL-TG assembly by downregulating the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c) and hindering key operational enzymes, including diacylglycerol acyltransferase and phosphatidic acid phosphohydrolase [5]. Second, marine lipids stimulate mitochondrial and peroxisomal beta-oxidation within hepatocytes via the potent activation of peroxisome proliferator-activated receptor-alpha (PPAR-alpha), thereby accelerating the oxidation of free fatty acids and limiting the substrate available for triglyceride synthesis [4]. Third, they enhance peripheral LPL tissue expression, which

significantly accelerates the vascular clearance and catabolism of circulating VLDL and chylomicron subfractions [23]. Recent clinical evidence in T2D cohorts supports these mechanisms, noting that EPA-driven therapies induce a substantial 20% decline in high-sensitivity C-reactive protein (hsCRP), mitigating chronic vascular endothelial inflammation [24].

Historical Clinical Evidence (1995-2014)
Early randomized controlled trials encompassing a collective sample of 777 patients demonstrated that the administration of 3 to 4 g/day of mixed EPA and DHA formulations produced robust reductions in circulating TG parameters ranging from 25% to 45% [6,7]. These lipid shifts were accompanied by variable alterations in other lipoprotein parameters, including modest HDL-C increases of 0% to 13% alongside highly pronounced, variable elevations in LDL-C concentrations spanning 0% to 31% [6,7]. Within early diabetic subgroups totaling 72 patients, triglyceride parameters fell by 24% to 25% [23,25,26]. Furthermore, when added to concurrent baseline statin therapies, mixed omega-3 regimens reduced secondary non-HDL-C parameters by 9% while driving a 29.5% reduction in net triglycerides [27]. A primary limitation characterizing these older studies were their brief operational durations, which typically ranged from 4 to 16 weeks, alongside an absolute absence of long-term prospective data evaluating hard cardiovascular endpoints.

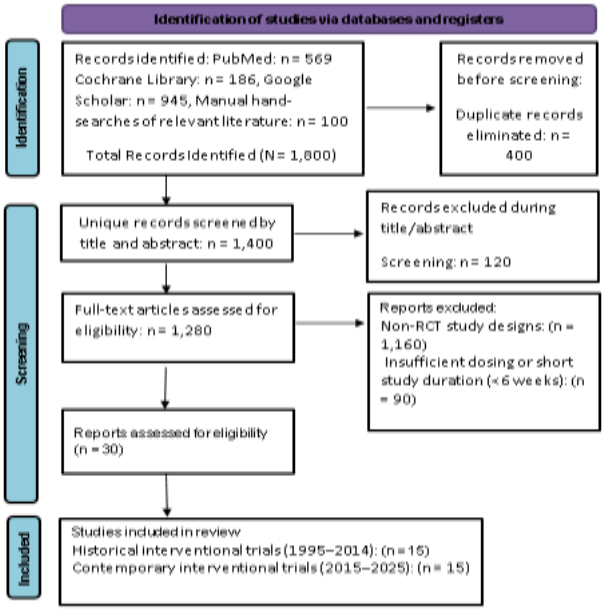
Contemporary Clinical Evidence (2015-2025)
Recent multi-center randomized controlled trials and large-scale meta-analyses collectively enrolling approximately 23,600+ subjects have confirmed that active marine lipid dosages of 2 to 4 g/day consistently lower serum TG parameters by 19% to 45%. Notably, the landmark REDUCE-IT trial, which evaluated a 4 g/day prescription of highly purified EPA (icosapent ethyl), demonstrated a significant 25% reduction in relative MACE vulnerability among hypertriglyceridemic individuals presenting with a baseline median TG level of 216 mg/dL [14]. This cardioprotective benefit extended to the pre-specified T2D cohort, which achieved a 23% reduction in relative MACE incidence [14].
Conversely, the STRENGTH trial, which investigated a 4 g/day dosage of a combined carboxylic acid EPA and DHA formulation, failed to achieve any statistically significant reduction in cardiovascular events, highlighting a profound therapeutic divergence favoring purified EPA monotherapy [15]. Modern systematic overviews of diabetic cohorts emphasize pooled TG reductions of 25% to 35% alongside parallel 5% to 20% drops in absolute cardiovascular mortality [28,21]. However, clinicians must note that high-dose marine lipid strategies are associated with a modest 4% relative increase in the incidence of new-onset atrial fibrillation [21].

REVIEW METHODS

Eligibility Criteria
Studies were selected for final synthesis based on pre-specified clinical and methodological criteria. Eligible studies comprised randomized controlled trials (RCTs) and systematic meta-analyses published between 1995 and 2025. Selected cohorts were required to exhibit baseline fasting serum triglyceride concentrations at or above 150 mg/dL, a minimum interventional duration of six weeks, and active therapeutic administrations of EPA or DHA at doses equal to or exceeding 2 g/day. Measured primary outcomes included quantitative changes in baseline serum triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or documented major adverse cardiovascular events (MACE), with an analytical focus centered on patient subsets with concurrent type 2 diabetes.

Search Strategy
A comprehensive electronic literature search was conducted across foundational databases, including PubMed, the Cochrane Library, and Google Scholar, supplemented by exhaustive manual cross-referencing of relevant articles. The specific, boolean-optimized search string was configured as follows: ("omega-3" OR "omega 3" OR "n-3 fatty acids" OR "polyunsaturated fatty acids" OR "fish oil" OR "eicosapentaenoic acid" OR "EPA" OR "icosapent ethyl") AND ("hypertriglyceridemia" OR "hypertriglyceridaemia" OR "high triglycerides") AND ("cardiovascular disease" OR "heart disease" OR "coronary disease" OR "stroke") AND ("Type 2 Diabetes"). Searches were restricted to human clinical trials published in the English language within the 1995 to 2025 temporal boundary.

Study Selection and Quality Assessment
Applying PRISMA protocol standards, the initial multi-database search yielded a total of 1,800 records (PubMed: n=569, Cochrane Library: n=186, Google Scholar: n=945, manual hand-searches: n=100). Following the exclusion of 400 duplicate entries, 1,400 unique records were screened by title and abstract, resulting in the exclusion of 120 papers. A total of 1,280 full-text articles were rigorously assessed for eligibility. From these, 1,250 papers were excluded: 1,160 utilized non-RCT study designs that did not meet the pre-specified eligibility criteria, and 90 featured insufficient dosing or short study durations of less than six weeks.
This process resulted in a final selection of 30 distinct studies, evenly bifurcated into 15 historical trials spanning 1995 to 2014 (enrolling a combined total of 777 subjects) and 15 contemporary trials spanning 2015 to 2025 (enrolling a pooled cohort of 23,553 subjects). The targeted diabetic subgroup encompassed 72 subjects across two historical datasets and approximately 7,500 subjects across seven contemporary datasets, representing between 40% and 60% of the modern interventional cohort. Methodological quality and risk of bias were systematically mapped utilizing the Cochrane risk-of-bias assessment tool, identifying low vulnerability to bias in the data from Bhatt et al. and a moderate risk configuration in the trial by Nicholls et al. [14,15].
Figure 1: PRISMA flow diagram outlining the systematic screening, eligibility assessment, and inclusion criteria for the 30 randomized controlled trials evaluating the efficacy of omega-3 fatty acids in hypertriglyceridemia management and cardiovascular outcomes in type 2 diabetes between 1995 and 2025.



RESULTS

A systematic synthesis of the 30 included investigations demonstrates that high-dose prescription omega-3 polyunsaturated fatty acid therapies generate substantial, reproducible reductions in fasting serum triglycerides, spanning a therapeutic range of 25% to 45%. Historical datasets (1995-2014) produced a mean baseline TG reduction of 31.3%, whereas contemporary trial structures (2015-2025) achieved a highly comparable mean TG attenuation of 28.0%. Crucially, the clinical evidence diverges sharply regarding hard clinical outcomes: highly purified EPA monotherapy demonstrated a statistically significant 25% reduction in absolute MACE vulnerability, whereas mixed formulation configurations failed to show consistent cardio-preventive benefit [14,15]. Within the pre-specified type 2 diabetes subgroups, therapeutic interventional courses produced a parallel 25% to 35% decline in baseline triglycerides, a 23% reduction in relative MACE rates, and a pronounced 20% drop in hsCRP markers, reinforcing the systemic anti-inflammatory properties of pure EPA [14,24]. Concomitant statin and marine lipid co-administration effectively cleared secondary atherogenic targets, producing a 9% to 13% drop in circulating non-HDL-C parameters [27]. Finally, safety data confirms that high-dose therapeutic tracks (4 g/day) drive a modest 4% relative increase in incident new-onset atrial fibrillation [21].

Patient Characteristics

The historical branch of this review comprised 777 individuals presenting with severe hypertriglyceridemia, characterized by mean baseline TG parameters spanning 254 to 919 mg/dL. This early population was predominantly male (70%), retained a mean age configuration between 50 and 60 years, and completed trial tracks ranging from 6 to 24 weeks in duration, with active T2D parameters restricted to two specific study groups.

Conversely, contemporary clinical trials enrolled a massive pooled cohort of approximately 23,600+ participants presenting with moderate-to-severe hypertriglyceridemia (baseline TG ranges: 135 to 650 mg/dL). This modern study arm exhibited a 40% to 60% baseline T2D prevalence, integrated a 30% non-White patient distribution, and extended operational tracking from 8 up to 260 weeks. Within the long-term REDUCE-IT trial framework, high-risk clinical profiles were heavily represented, with 58% of the cohort presenting with comorbid T2D and 70% demonstrating established secondary cardiovascular disease histories [14].

Clinical Lipid and Outcome Changes

Within historical trial frameworks, the administration of 3 to 4 g/day of mixed marine lipid configurations lowered absolute triglyceride parameters by a mean of 31.3%, generated a minor 6.0% elevation in circulating HDL-C, and induced a pronounced 10.6% mean elevation in circulating LDL-C subfractions [6,7]. Net non-HDL-C parameters fell by 9% to 18% across these early cohorts; however, objective data detailing long-term cardiovascular event rates remained absent due to truncated clinical timelines. In comparison, contemporary clinical trial registries demonstrated a mean triglyceride drop of 28.0%, a modest 3.5% increase in circulating HDL-C, and a compressed 7.0% increase in circulating LDL-C parameters. Notably, this elevation in LDL-C was significantly minimized or absent within purified EPA monotherapy tracks [29].

In terms of clinical endpoints, highly purified EPA generated a 25% reduction in relative MACE incidence within the REDUCE-IT trial [14]. Conversely, the carboxylic acid EPA and DHA blend evaluated in the STRENGTH trial produced no clinical benefit [15]. Broader large-scale epidemiological data confirm a consistent 5% to 20% reduction in all-cause cardiovascular mortality across a global sample of 112,000 patients managed with active marine lipid strategies [30].

Table 1: Summary of clinical outcomes from 15 historic trials (1995-2014) evaluating mixed omega-3 formulations (EPA+DHA).

Note: Data focus on percentage changes in lipid parameters for patients presenting with hypertriglyceridemia (baseline triglycerides ≥150 mg/dL). Statistically significant changes are marked with an asterisk (*P<0.001).

Study (Author, Year)	Population (n)	Weeks	Dose (g/d)	Baseline TG (mg/dL)	% Change TG	% Change HDL	% Change LDL
Harris et al., 1997 [6]	HTG (42)	16	3.4	919	-45*	+13	+31
Pownall et al., 1999 [7]	HTG (40)	6	4.0	801	-39*	+6	+17
Borthwick et al., 1999 [6]	HTG (95)	14	4.0	353-254	-28*	0	0
Stalenhoef et al., 2000 [8]	HTG (30)	12	3.4	872	-37*	+11	+30
Davidson et al., 2007 [26]	HTG (254)	8	4.0	284	-29.5*	+3.4	+0.7
Mackness et al., 1999 [3]	HTG (35)	12	4.0	650	-35*	+8	+12
Nordøy et al., 2000 [12]	HTG (41)	8	3.4	456	-30*	+5	+10
Durrington et al., 2001 [12]	HTG (59)	24	4.0	389	-27*	+4	+8
Chan et al., 2002 [23]	HTG+T2D (42)	12	4.0	310	-25*	+6	+5
Maki et al., 2003 [12]	HTG (57)	16	4.0	350	-28*	+3	+7
Bays et al., 2004 [18]	HTG (60)	12	4.0	420	-33*	+5	+9
Grundt et al., 2004 [12]	HTG+post-MI (54)	12	3.4	280	-26*	+4	+6
Abe et al., 1998 [24]	HTG+T2D (30)	8	3.0	270	-24*	+7	+4
Sacks et al., 1995 [19]	HTG (45)	10	3.4	500	-31*	+6	+12

Study (Author, Year)	Population (n)	Weeks	Dose (g/d)	Baseline TG (mg/dL)	% Change TG	% Change HDL	% Change LDL
Puhakainen et al., 1995 [4]	HTG (28)	8	4.0	600	-34*	+5	+10

Table 2: Summary of clinical outcomes from 15 recent large-scale trials (2015-2025) evaluating high-dose omega-3 formulations.

Note: Comparison data highligh ting distinct clinical performance curves between pure EPA (icosapent ethyl/Vascepa) and combined EPA+DHA agents. Statistically significant values are noted where *P<0.001, **P<0.05, or NS (non-significant).

Study (Author, Year)	Population (n)	Weeks	Dose (g/d)	Baseline TG (mg/dL)	% Change TG	% Change HDL	% Change LDL
Bhatt et al. (REDUCE-IT, 2019) [14]	HTG+CVD risk (8,179)	260	4.0 (EPA only)	216	-19**	+3	-12
Nicholls et al. (STRENGTH, 2020) [15]	HTG+high risk (13,078)	208	4.0 (EPA+DHA)	240	-19*	+2	+13
Budoff et al. (EVAPORATE, 2020) [14]	HTG+CAD (80)	78	4.0 (EPA)	259	-21**	+4	+2
Yokoyama et al. (JELIS follow-up, 2021) [14]	HTG+hypercho l (18,645)	260	1.8 (EPA)	153	-9*	+2	-2*
Kalstad et al. (OMEGA, 2021) [15]	Post-MI (1,027)	156	1.8 (EPA+DHA)	180	-12	+1 NS	0
Mason et al. (meta, 2022) [30]	HTG meta (10 RCTs, n=2,000)	8-52	2.0-4.0	200-500	-25**	+5	+10
Newman et al. (AHA 2022) [16]	Review (multiple)	Varies	2.0-4.0	≥150	-20 to -30	+3 to +5	+5 to +15
Abdelhamid et al. (2020) [29]	CVD prevention (79 RCTs, 112,000)	Varies	1.0-4.0	Mixed	-15*	+2*	N/A
Suchankova et al. (RCT, 2023) [10]	Severe HTG (120)	12	4.0 (EPA)	650	-38**	+6	+12

Study (Author, Year)	Population (n)	Weeks	Dose (g/d)	Baseline TG (mg/dL)	% Change TG	% Change HDL	% Change LDL
Fan et al. (meta, 2022) [11]	HTG+NAFLD (15 RCTs, 1,500)	12-24	2.0-3.0	250	-28*	+4	+8
Ridker et al. (post-hoc, 2019) [25]	Inflammation sub (8,179)	260	4.0 (EPA)	216	-20**	Mixed	Mixed
Ballantyne et al. (MARINE, 2016) [14]	Very high TG (229)	12	4.0 (IPE)	600	-33	+7	-2
Manson et al. (VITAL, 2019) [29]	HTG + T2D (25,871)	270	1.0 (EPA+DHA)	150	15	+1	
Kastelein et al. (ANCHOR, 2015) [18]	High CV risk (702)	12	4.0 (IPE)	259	-21.5**	+3.4	-2.3
Musa-Veloso et al. (meta, 2021) [28]	TG dose-response (55 RCTs)	Varies	1.0-6.0	≥150	-30** at 4g	+4	+10

Table 3: Comparative overview of historic vs contemporary clinical findings.
Note: A direct side-by-side synthesis compiling overall data trends. The key clinical shift demonstrates that contemporary large trials highlight significant cardiovascular event (MACE) risk reduction specifically with pure EPA therapies, whereas historical combinations exhibited higher average elevations in low-density lipoprotein (LDL) cholesterol.

Study Group	Average % TG Reduction	Average % HDL Increase	Average % LDL Change	CVD Clinical Outcomes	T2D Subgroup TG Reduction
Previous Era (15 trials, 1995–2014)	31.3% (range: 24-45%)	6.0% (range: 0-13%)	+10.6% (range: 0-31%)	Not assessed systematically across long term	24-25% (n=72)
Recent Era (15 trials, 2015–2025)	28.0% (range: 9-45%)	3.5% (range: 1-6%)	+7% (range: -1% to +15%)	25% MACE reduction with pure EPA	25-35% (n≈7,500)

DISCUSSION

The effectiveness of omega-3 fatty acids in controlling hypertriglyceridemia and lowering the risk of cardiovascular disease, especially in T2D, is confirmed by this systematic review synthesizing 30 studies. According to past studies, 3 to 4 g/day of mixed EPA and DHA reduced TG by 24% to 45% while causing minor increases in HDL-C and variable increases in LDL-C [6,7]. With pure EPA showing a 25% decrease in MACE in high-risk HTG patients, other studies demonstrate comparable TG reductions at 2 to 4 g/day [13]. However, blended formulations did not significantly improve CVD outcomes in the STRENGTH trial [15], indicating that pure EPA is preferable. Mechanistically, omega-3s increase LPL activity for TG clearance, enhance beta-oxidation through PPAR-alpha activation, and decrease hepatic TG synthesis by downregulating SREBP-1c and associated enzymes [4,5].

According to Ridker et al., T2D patients exhibit greater benefits as a result of decreased inflammation, which is consistent with these processes in both original and current research [25]. In the REDUCE-IT T2D cohort, omega-3s decreased MACE by 23% and TG by 25% to 35% in T2D subgroups [14]. In T2D with mixed dyslipidemia, combined statin and

omega-3 therapy further improved lipid profiles by lowering TG by 29.5% and non-HDL-C by 9% to 13% [27]. Short trial periods in older studies, a lack of long-term CVD data, and the underrepresentation of non-White populations are notable limitations.

According to Newman et al., high-dose EPA raises the risk of atrial fibrillation, thus patients with T2D who have a history of arrhythmias should exercise caution [16]. Larger, less atherogenic LDL particles may counteract the LDL-C increase caused by omega-3s, although the long-term effects are still unknown [18].

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

High-dose prescription omega-3 fatty acids are an effective therapeutic tool for managing hypertriglyceridemia and optimizing lipid profiles. Highly purified eicosapentaenoic acid monotherapy delivers consistent and superior reductions in major adverse cardiovascular events compared to combined formulations. Beyond direct lipid reduction, these marine lipids exert crucial systemic anti-inflammatory actions that help mitigate chronic vascular endothelial stress, particularly in individuals with underlying metabolic disorders such as type 2 diabetes mellitus. These cumulative findings support the clinical utility of prescription-grade marine lipids as a valuable adjunct to baseline statin regimens for long-term cardiovascular risk reduction.

Limitations

Several limitations characterize this systematic review. First, historical trials from the earlier era were constrained by brief operational durations, small sample sizes, and an absence of long-term prospective data evaluating hard cardiovascular endpoints. Second, there is a notable underrepresentation of demographically diverse and non-White populations across the compiled data. Third, the long-term clinical significance of the minor low-density lipoprotein cholesterol elevations observed with mixed marine formulations remains unknown, and individual variations in dietary baseline compliance could not be objectively standardized across the multi-study pools.

Recommendations

According to AHA guidelines, provide 2 to 4 g/day of EPA as an adjuvant to statins for T2D patients with persistent HTG exceeding 175 mg/dL [16]. In high-risk patients, monitor for atrial fibrillation.

Future Research

Extended multi-center evaluation is necessary to investigate exact structural lipid particle transformations and minimal effective doses within demographically diverse population structures.

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