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# Blending of Omega-3 Fatty Oils and Statin Therapy in Hyperlipidemia: A Multicentric Integrative Route

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## Abstract:
***The prevalence of hyperlipidemia still continues to be a major risk factor when it comes to cardiovascular diseases, regardless of the statin use. In this multicenter prospective interventional study, the authors intended to examine the effect of an oceanic combination of omega-3 fatty acids (2 g/day) with statin therapy in a population of patients with refractory hypertriglyceridemia. As conducted in three tertiary care facilities in Lebanon, Sweden, and Norway, 180 patients were enrolled in the study with 12 weeks of randomization into either a combination therapy group or statin-only group. The key measure was the change in proportion of serum triglycerides and secondary measures were LDL-C, HDL-C, high-sensitivity C reactive protein (hs-CRP) and adverse events pattern. Combination therapy led to 26.7 percent decrease of triglycerides, 10.8 percent in control group ($p < 0.001$). There were also increases in the levels of HDL-C and hs-CRP. Major safety considerations were not cited. The two findings corroborate the idea of combining omega- 3 supplementation with statin medication as an effective measure of ensuring that the lipid levels of the hyperlipidemic patients are optimized.***

**Keywords:** ***Hyperlipidemia, Omega-3 fatty Acids, Statin Therapy, Combination Therapy, Hypertriglyceridemia, Triglycerides, LDL-C, HDL-C, hs-CRP, Cardiovascular Diseases, Nutraceuticals.***

## 1. Introduction
The presence of altered high-levels of lipids, especially triglycerides and low-density lipoprotein cholesterol (LDL-C) leading to hyperlipidemia is a major health problem and a key modifiable risk factor of cardiovascular disease (CVD) that has existed across the world. Nevertheless, the high rate of cardiovascular diseases such as heart attacks, strokes and other atherosclerotic diseases is still seen despite pharma technological advances toward treating hyperlipidemia. The question of hyperlipidemia-related CVD is quite clear, and it is possible to highlight that the presence of persistent hypertriglyceridemia is extremely difficult to resolve. Statins, which are the most popular treatments in terms of hyperlipidemia are still the focus of treatment, yet, unfortunately, the majority of patients do not exhibit optimum control over lipids and more importantly triglycerides. There is a now growing evidence that omega-3 fatty acids, commonly termed as nutraceuticals can give extra lipid lowering and anti-inflammatory effects. This introduction supports the introduction with the burden of hyperlipidemia, the inability of statin monotherapy, the benefits of omega-3 fatty acid, and the reasons on the need to undertake a combination therapy to help manage lipid levels in patients demonstrate persistent hypertriglyceridemia.

### 1.1. Burden of hyperlipidemia and its contribution to the risk of cardiovascular disease
Hyperlipidemia constitutes one the commonest risk factors of cardiovascular disease (CVD), increased triglycerides and levels of LDL-C have been associated with the occurrence of atherosclerosis, fatty formation and endothelial dysfunction. Despite new strategies that have been developed to offer help about CVD, it continues to be the greatest cause of morbidity and death all over the globe, triggering millions of deaths every year. Even with the recognized involvement of hyperlipidemia in the pathophysiology of CVD, many remain with abnormal levels of lipids, particularly triglycerides, despite effective intervention and lipid-lowering therapy.(1)
The chronic hypertriglyceridemia (higher than 150 mg/dL of triglycerides) is especially worrying, since it is characterized by the expanded possibilities of IAM and pancreatitis occurrence along with other metabolic disorders. Patients who have high triglycerides predisposition are likely to have associated metabolic problems and these include insulin resistance, obesity and hypertension which collectively increase cardiovascular risk. Whereas statins are very effective regarding LDL-C reduction, they do not play significant roles regarding triglycerides, and this calls upon the use of complementary therapies of triglycerides and inflammation.

### 1.2 Weaknesses of statin monotherapy: persistent hypertriglyceridemia

Statins (atorvastatin, simvastatin, rosuvastatin) can be referred to as the gold standard to treat hyperlipidemia. They are proven to lower LDL-C hence minimizing atherosclerotic cardiovascular events. Nevertheless, being useful in reducing the LDL-C concentration, the statins cannot be as helpful in managing high amounts of triglycerides and partial ameliorating the lipid profile among patients with hypertriglyceridemia. As an example, statins tend to have a small triglyceride lowering effect with decreases observed usually between 10-20 percent. This is especially concerning in those with high triglycerides in whom residual cardiovascular risk remains in the face of optimal statin therapy.

It is also possible that statin therapy could not mitigate all of the underlying of CVD, nonparticularly, high-sensitivity C-reactive protein(hs-CRP), which is an inflammatory marker correlated to plaque vulnerability and heart vulnerability. Such restrictions emphasize the necessity of creating a more holistic solution, which may take the form of subsequently incorporating omega-3 fatty acids to affect lipids, as well as inflammation, at the same time.(2)

### 1.3 Evidence-Based Use of Omega 3 in Lipids and Reduction of Inflammation

Essential polyunsaturated fatty acids are omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are required in the diet because they have a high level of lipid-reducing and anti-inflammatory effects. Various researches have shown that omega-3 fatty acids have the potential to lower serum triglyceride tremendously, particularly between 20% to 30% in patients who have high triglyceride levels. There is also an effect of omega-3 fatty acids on the lipid profile with an elevated level of high-density lipoprotein cholesterol (HDL-C), which reverses the transport of cholesterol and minimizes the threat of plaque formation.

Besides lowering lipids, omega-3 fatty acids have been known to alter an inflammatory pathway that plays an important role in CVD pathogenesis. They also lower the hs-CRP, a main indicator of systemic inflammation in an individual since they suppress the production of pro-inflammatory cytokines and increase anti-inflammatory cytokines. The anti-inflammatory and lipid-lowering effects rendered such lipid-lowering agents as omega-3 fatty acids an appealing adjunctive therapy to statins, especially in those with recalcitrant hypertriglyceridemia and a state of continued inflammation.

### 1.4 Reason behind Combination Therapy Approach

Since the therapeutic effect of omega-3 fatty acids and statins can be described as compliments, combination therapy is an interesting prospect to maximize lipid control in hyperlipidemia patients. Whereas statins work in battling LDL-C and thus decreasing the collection of cholesterol in blood vessels, the use of omega-3 fatty acids can supplement that effect by decreasing the level of triglycerides, stimulating the concentrations of HDL-C, and diminishing inflammation, which are major contributors to the emergence of atherosclerosis. A combination of these treatments may increase lipid management, reduce the residual cardiovascular risk and outcome.

The strategy will be useful especially on people with persistent Hypertriglyceridemia, as they never manage to obtain adequate triglyceride reduction when taking statin as monotherapy. There is evidence of synergistic effects of the combination of both omega-3 fatty acids and statins in providing better lipid profile as well as vascular inflammation, which is an added advantage over the use of statins alone in managing the risk of cardiovascular diseases.

### 1.5 Study Purpose: To ask e Efficacy and Safety of Add-On of High-Purity, Omega-3 Fatty Acids to Statin Treatment

The main objective of this multicentric trial is to evaluate whether high-purity omega-3 fatty acids (2 g/day) on top of standard statin therapy of patients with persistent hypertriglyceridemia is effective and safe. The changes of serum triglyceride level will be used as the primary endpoint, whereas the change of LDL-C, HDL-C, and hs-CRP will be secondary endpoints, as well as the adverse event. The proposed study will add valuable evidence of the usefulness of combination therapy in enhancing the control of lipids and inflammation in hyperlipidemia patients, which will ultimately lead to increased effectiveness of risk reduction of cardiovascular diseases.(3)

## 2. Intervention Protocol and Study Protocol

This is a detailed protocol in the study on the efficacy and safety of using combination therapy of omega-3 fatty acids with statin in patients with persistent hypertriglyceridemia. It is a multicentered, prospective interventional study that will take place in three Lebanese, Swedish and Norwegian tertiary care centers. It seeks to determine the levels in which the combination therapy scores on lowering the serum triglyceride level and its ability to improve other cardiovascular risk markers compared to statin alone.

**2.1 population: Inclusion/Exclusion Criteria of Adults having Persistent Hypertriglyceridemia**

The adults who have had persistent hypertriglyceridemia were included in the study as the target population and were defined as individuals with serum triglyceride concentration of above 200 mg/dL despite statins therapy. The individuals included in the study were recruited in three tertiary care centers, in Lebanon, Sweden, and Norway. The next inclusion and exclusion criteria were used, thus making the study population representative of patients who had persistent lipid abnormalities despite routine treatment methods.

Inclusion Criteria:

- Age: The participants of the research are to be 18 years and older.
- Diagnostic criteria of Hyperlipidemia: All participants have to have persistent hypertriglyceridemia (levels were >200 mg / dL), even after admission to stable doses of statins with at least 3 months of participation.
- Stable Statin Therapy: Each and every subject will be placed under statin Therapy (either atorvastatin, simvastatin or rosuvastatin) with a stable dose (at least 3 months) prior to their participation in the study at the time of enrolment.
- Intention to Participate: Patients have to sign an informed consent form and be willing to adhere to the research regulations, follow-ups and proceed with the intervention.

Exclusion Criteria:

- Severe Hyperlipidemia Patients were not included with severe hypertriglyceridemia ( triglycerides >1000 mg/ dL) or patients with secondary causes of hyperlipidemia (diabetes mellitus, chronic kidney disease, hypothyroidism).
- Serious Comorbidities: Possible comorbidities that can interfere with study protocol, including lack of control in diabetes, liver disease, renal failure, or heart failure, were considered. It should be avoided by excluding participants with serious comorbid conditions.
- Pregnancy or Breastfeeding: Pregnant women were not to participate, as well as the ones who were breastfeeding or planned to become pregnant during the study.
- Omega-3 Fatty Acids Allergy: Patients with the history of allergy to omega-3 fatty acids, or any of the components in the formulations were excluded.

**2.2 Multicenters: Tertiary Care Centers of Lebanese, Swedish and Norway**

The research was carried out in three tertiary care units found in Lebanon, Sweden and Norway. Recruitment, data collection and follow-up was the responsibility of each center. This was made possible by the multicenter method used, which enabled using a heterogenous population of patients, and thus increased the generalizability of the findings. Data collection methods including the outcome of the study and the intervention process were uniform across all the centers thus ensuring the study protocol was standardized in all the centers.

The variety of centers allowed also evaluating how various healthcare systems and geography influence the changes in adherence to treatments and lipids maintenance. This method enhanced the external validity of the study and therefore the findings would apply the results to a larger number of patients with hyperlipidemia.

**2.3 Intervention groups**

They became randomized into any of two groups:

**2.3.1 Combo Therapy -Omega-3 Fatty Acids (2 g/day) / Statin:**

- The omega-3 fatty acids used were 2 g/day taken as high purity fish oil supplements that included eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
- The subjects in this group managed to maintain their stable statin dosing regimen and they were given 2 g/day of omega-3 fatty acids. The omega-3 fatty acids were reduced in the amount of 1 g and split into two doses to be taken with meals to reduce gastrointestinal symptoms.
- This combined treatment was used because the use of omega-3 fatty acids is known to reduce lipids, mainly triglycerides and increase good cholesterol (HDL-C).

**2.3.2 Lack of control Lack of control: Statin Therapy alone:**

The control group was then given standard statin therapy administered in a stable statin dose (atorvastatin, simvastatin or rosuvastatin) during the 12 weeks of study.

The control group presented the basis according to which it was possible to measure the extra advantage of omega-3 supplementation in addition to statin treatment.

Both groups were to carry on with their usual change in lifestyle, such as dietary advisement and workout prescription, which was communicated to every respondent as standard care.

**Intervention lengths 12 Weeks 2.4 Weeks**

The intention to take up the same period of intervention through the course of the 12 weeks was used to give ample time to give the omega-3 fatty acids to produce effects on lipid metabolism and the inflammatory markers. The duration of a 12-week period is aligned to the existing literature of observing the anti-lipid changes of omega-3 fatty acids, and statins when it comes to patients with hyperlipidemia. Ongoing statin therapy was involved in the administration of the intervention to determine possible synergistic effects between the two therapies.(5)

Participants came to a final evaluation at the end of the study dive, which consisted of measuring the serum triglycerides, LDL-C, HDL-C, and hs-CRP.

**2.5 Standard Care and Dietary Counseling as Part of a Combination**

Besides the main interventions, all the subjects were provided with concomitant standard care, which included dietary counseling aimed at maximizing the management of lipids. The food advice was on decreasing the amount of saturated fat, increasing the consumption of omega-3 sources (e.g., healthful seafood, flaxseeds), and encouraging exercise, in support of total cardiovascular health. Although the purpose of the study was to assess the effects of omega-3 supplement and statin treatment, these lifestyle changes were consistent to all those participating in the study as the effects noted could be connected to the interventions and not changes in lifestyles or eating habits.

**2.6 Informed Consent and Ethical Section**

The studies conducted were attended by their institutional review board (IRB) in each of the centers involved. The study was approved ethically meaning that it conformed to all the regulatory and ethical requirements towards undertaking clinical trials. All the participants have signed informed consent before enrollment and explanations were given about the purpose of the study, the procedures, informations about potential risks or benefits.

Respondents were disclosed, they had the right to quit the investigation at any moment without affecting further treatment and care. Any data on patients were treated as confidential and there were no human ethical violations of any kind followed in the study.

## 3. Study Methodology and Design

The given section gives a thorough description of the study design, methodology, and statistical approach used to introduce the study aimed at assessing the efficacy and safety of the combined use of omega-3 fatty acids and statins in patients diagnosed with persistent hypertriglyceridemia. The research protocol is of multicenter prospective interventional type, which allows the high-quality data to be collected at various geographical locations; thus promoting the overall applicability of the results garnered. The given sections explain the randomization procedure, the endpoint definitions, the laboratory measurements and the plan of statistical analysis of the study.

**3.1 Prospective Interventional Multicentric study**

It was a multicenter prospective interventional trial and three tertiary care centers from Lebanon, Sweden and Norway participated in the study. The multicentric design was important to the study, as it was used to increase the variety and generalizability of the study population to cover a wider usage of the results to various healthcare institutions as well as different regions. All centers were operated under the same standardized protocol guaranteeing consistency in data gathering, management of a patient, and delivery of the interventions.

The experimental design was prospective and entailed the possibility of obtaining real-time information regarding the effects of administration of omega-3 fatty acids, and statins combination, on a 12-week intervention schedule. The cause-and-effect relationships can be evaluated with this design, as well as the interventional character of the study will also guarantee that the resulting outcomes changes can be directly related to the combination therapy.

**3.2 Randomization process, and allocations ratio**

The participants were randomly distributed to two groups of the interventions: combination therapy (omega-3 fatty acids in combination with statin) and statin monotherapy (control group). To perform the randomization process unbiasedly, the list of randomization was generated by computer. The randomization was done on one to one ratio and this implied that the number of participants in the two groups is equal to ensure fair comparison between the two interventions.(6)

Participants and investigators did not know the group allocation to determine blinding, also referred to as single-blind randomization. This assists in the minimization of bias and placebo effect in the study outcomes. The process of allocation was not revealed to the clinicians and research personnel involved in the enrolment, and so, treatment allocation was entirely random and neither of the investigators or the subjects could sway the process.

**3.3 Primary End point: % Change of strel triglycerides-levels**

Change in the level of serum triglycerides was determined as the main outcome measure of the study expressed as a percentage change between baseline and the conclusion of the study period of 12 weeks. The selection of the primary endpoint was based on the fact that triglyceride is a significant player in the pathophysiology of cardiovascular disease and a key indicator when it comes to treating hyperlipidemia. A high concentration of triglycerides is a robust independent risk factor of atherosclerotic cardiovascular disease and pancreatitis.

Blood samples were drawn at baseline level (pre-intervention), week 4, and at the 12-week follow-up to determine the level of triglycerides. Percentage changes of triglycerides were estimated in each of the participants and the group level difference between combination therapy group and statin only group has been analyzed. The reduction in the triglycerides in the combination therapy group would be significant and this would signify the potential effectiveness of the adjuvant omega-3 supplementation to statin in the management of triglycerides.

**Secondary endpoints: LDL-C, HDL-C, hs-CRP, and Adverse event Profiles**

Along with the primary endpoint, there were multiple secondary endpoints so that a total picture of the combination therapy effects on the lipid metabolism and inflammation could be represented. Such secondary endpoints included:

LDL-C (Low-Density Lipoprotein Cholesterol): Measurement of LDL-C which is commonly known as the bad cholesterol was taken at the baseline and 12 weeks after to determine whether there was an effect of the combination therapy on the state of cholesterol. Statins do have a significant effect in reducing LDL-C and additional or complementary effects might be achieved through addition of omega-3 fatty acids.

HDL-C (High-Density Lipoprotein Cholesterol): HDL-C (or high-density lipoprotein cholesterol) is, in essence, the good cholesterol level, which helps in cleaning the amount of cholesterol that has accumulated in the body. HDL-C is usually good when the levels increase. The impact of omega-3 fatty acid on levels of HDL-C was measured as the study compared levels of HDL-C measurements at baseline and at 12 weeks.

hs-CRP (High -Sensitivity C Reactive Protein): hs-CRP is a pertinent marker of mass -dismissive inflammation and past related with raised risk of vascular incidents. The research was conducted to calculate the anti-inflammatory cost of omega-3 supplements on the back of statin drug therapy. The levels of hs-CRP at the baseline and the presentation after 12 weeks were measured to determine the level of anti-inflammatory responses of the supplements to statins.(7)

Adverse event profile: profile of adverse events was also monitored and recordings were noted during the intervention period too. During follow-up visits, patients were asked to report side effects and any health complications, and adverse events considered by patients as mild, moderate, or severe. The safety of the combination therapy was determined by comparison of incidence and character of any adverse event arising between the two groups.

**3.5 Quality control and measurements in the laboratory**

As a means to facilitate quality and validity of the outcomes, each of the participating centers performed all laboratory measurements in accredited clinical laboratories. Standardized techniques in laboratory measurement were used in determining level of triglyceride/LDL-C, HDL-C and hs- CRP, and any units were measured in duplicates in case of errors. Quality control was taken care of by regular control procedures to maintain the consistency of test results among the three centers. Besides, the analysis of the samples was carried out by blinded laboratory personnel to uphold objectivity in the measurement of outcomes.

**3.6 Between Group statistical plan of analysis**

Statistical analysis aimed at the comparison of the efficacy between the combination therapy and monotherapy with statins by the primary and the secondary endpoints. The main analysis was the calculation of the percent change in serum triglycerides between the two groups compared with the independent t-tests or analysis of covariance (ANCOVA) examination of the mean difference between the groups of the triglyceride changes by the adjustment of the baseline levels of triglyceride.

In the secondary endpoints, the difference in LDL-C, hs-CRP, HDL-C and the adverse events between the two groups were also compared using t-tests and chi-square test respectively in the case of the continuous and

categorical variables (adverse event occurrence). All the analyses were deemed statistically important with p-value less than 0.05.

Subgroups analysis was done to assess the outcomes of combination therapy within subgroups of patients having varying baseline triglyceride level and statin therapy. All the analyses were carried out with the help of SPSS or other statistics packages.

## 4. Results

The section presents the conclusion of the core of the study examining the effectiveness and safety of the use of omega-3 fatty acids and statins to treat the patients with sustained hypertriglyceridemia. The main outcome of the analysis entailed a decline in serum triglycerides, and other secondary outcomes were HDL-C, hs-CRP, LDL-C, adverse events, and tolerability. Generally, the individual investigation proved that the combination therapy of omega-3 supplementation led to a significant impact on lipid profile and improvement of inflammatory factors when compared with statin therapy only.

### 4.1 Descriptive study subjects characteristics at baseline

At baseline, the 180 subjects (n=90 in each group) were quite similar in age, gender, and baseline lipid levels, and other clinical parameters. The average age of the respondents was 58 years, half of them were men (52%) and half women (48%). The majority of the participants possessed chronic hypertriglyceridemia, and baseline levels of serum triglycerides were 240 mg/dL on average in both groups. The participants were put on a stable treatment (atorvastatin, simvastatin, or rosuvastatin) of statins treatment, and this was 3 months and more before they could be enrolled. Comparison between the two groups on the level of baseline LDL-C, HDL-C, hs-CRP was done and show no significant differences to ensure the compare of the two groups as the study began.

These were subjects with a past history of cardiovascular risk factors like hypertension, diabetes, and obesity hence this cohort was a high-risk population in regard to cardiovascular events. Its baseline attributes displayed a group of individuals who could use more vigorous treatment of dyslipidemia and inflammation.(8)

### 4.2 Note Outcome 1 Primary: Percent Triglyceride Reduction Triglyceride-Reduction 26.7(Combination) 10.8( Control) $p < 0.001$

The percentage change in serum triglycerides achieved the lowest p value of the study, that is, it significantly varied between the groups. The hierarchy of the groups based on the triglyceride level as the mean decreased by 26.7 percent of baseline (this was the combination therapy group: omega-3 + statin) and by 10.8 percent of baseline (this was the statin-only group) ($p < 0.001$).

Further support of the benefit of adding omega-3 fatty acids to statins in lowering triglycerides is the observation that triglycerides were lowered 16% more in the combination group. This drastic decline in serum triglycerides by the combination therapy group implies that omega-3 supplementation has a potential use as an encouraging supplement to statins in treating hypertriglyceridemia, especially in patients who continue to experience significant cardiovascular risk despite the use of statins.

### 4.3 Combination Group had increased HDL-C than Control

The effects of combination therapy on the levels of HDL-C carried an important secondary endpoint value, as it can play roles in protecting against atherosclerotic cardiovascular disease. The combination therapy group had a marked increase in HDL-C level with a mean of + 5.3 percent at baseline compared to statin alone that only increased by + 1.2 percent at baseline ($p < 0.05$).

This observation is in line with earlier studies that have reported on the ability of omega-3 fatty acids to raise HDL-C, which, in many cases, tends to offer protection against any cardiovascular disease. Statins mainly reduce LDL-C, but omega-3 supplement increased HDL-C levels promote the combination therapy case in dyslipidemia patients.

### Falling hs-CRP Falling hs-CRP Omega-3 Supplementation

A secondary endpoint was also reduction in level of a marker of inflammation, high-sensitivity C-reactive protein (hs-CRP), which is related to greater cardiovascular risk. The combination therapy group also had a significant decrease in the levels of hs-CRP with a 21 percent decrease against the baseline ($p < 0.01$). Conversely, hs-CRP was reduced to a lesser degree of 5% ($p = 0.1$) in statin-only group.

The substantial hs-CRP lowered in the omega-3 group substantiates the anti-inflammatory impacts of the omega-3 fatty acids which can possibly alleviate the congenital inflammatory processes that lead to atherosclerosis and

plaque instability. This shows that there is an additionality of omega-3 supplementation with statins regarding the value of these two groups in relation to vascular health improvements besides the enhancement of lipid levels.

**4.5No significant divergent factors of reduction of LDL-C were observed between the groups.**

Both the groups indicated significant improvements in LDL-C levels, whereby the former indicated a mean reduction of 22%, in comparison to the latter having an improvement of 23%, on average ( $p = 0.56$ ). The groups did not differ in any substantial way regarding LDL-C lowering, and it can be stated that solely statins were just as well as effective regarding lowering LDL-C levels in both combinations and the statin-only groups.

This observation implies that the omega-3 supplementation did not counteract the lipid-lowering effect of the statins on LDL-C yet had add-on effects on triglycerides and HDL-C and inflammation.(9)

**4.6 Safety Profile: Not Relevant; Major Adverse Events are not of concern; Tolerability assessment**

Safety profile of interventions was also monitored, and it was focused on adverse events (AEs) and tolerability. On average, the two groups were tolerating the treatments well and no serious adverse events occurred. These adverse events mostly included mild gastrointestinal related problems that included nausea and bloating that was experienced in minimal groups of participants (5 percent in the combination regimen group and 3 percent in the statin only group). These caused temporary problems and were cured without medical treatment.

No severe adverse events were reported (e.g., muscle pain, hepatic toxicity, or cardio events), and this indicates that omega-3 fatty acids and statins combination therapeutic method could be safe and well-tolerated during the length of the change in 12 weeks.

**4.7 Adherence in the Two Study Arms**

In the combination therapy group and the statin-only, the intervention adherence was high with 95 percent of the participants in both groups reporting that they were more than 80 percent adherent to their designated drug regimen. The adherence was ensured by counting pills at the visits and the reports of the patients. The rationale of the high compliance rates addresses the possibility of omega-3 supplementation with statin treatment in routine care in the management of hyperlipidemia.

## 5. Discussion

The results of the research that tested the effectiveness of omega-3 fatty acids as an add-on to statin treatment in patients with chronic hypertriglyceridemia can serve as a useful piece of information in the fields of treating lipids and controlling the occurrence of inflammation. The combination treatment showed great changes in the triglycerides, HDL-C, and the level of inflammatory markers like hs-CRP, even when the effect of statins on the LDL-C levels was retained. This discussion puts into perspective the clinical implications of such finding, its comparisons to previous studies, and how researchers can pursue it in future.

**5.1 An Interpretation of Triglyceride and HDL- C Improvements Clinically**

The major finding of the study was mentioning that the triglyceride levels were lowered by 26.7% in the combination therapy group; a significant change when compared to the 10.8% change in statin-only group. This implies that supplementation of omega-3 fatty acids is a significant plus to the hypertriglyceridemia patients, particularly when the hypertriglyceridemia patients have not stabilized on statins therapy. High-level serum triglyceride is a known risk factor of cardiovascular events and this observation justifies the use of omega-3 supplementation as adjunct therapy to the management of the residual cardiovascular risk in such individuals.

Further, the fact that the combination therapy group improved the levels of HDL-C (mean of 5.3%) is notable as well. HDL-C, or good cholesterol, is vital in reverse cholesterol transport that can remove peripheral excess cholesterol into the liver to be disposed of. Raising HDL-C is usually linked to a reduction in cardiovascular risk, and it could be that improvement in HDL-C by omega-3 fatty acids offers an added defence alongside reduction of LDL-C by statins.

The overall decrease in triglycerides and an apparent raise in HDL-C levels makes omega-3 supplementation an extremely useful tool to include in the management of dyslipidemia patients due to the significant improvement in the quality and count of the lipids profile in a fashion statins are not capable of accomplishing alone.

**5.2 Omega-3 role of anti-inflammation in cardiovascular risk mitigation**

Besides lipid modifying effects, some of these fatty acids such as omega-3s possess strong ant-inflammatory qualities. The 21 % hs-CRP lowering in the combination therapy group indicates that omega-3 supplementation may have both lipoprotein improving and anti-inflammatory effects; which is deemed as the critical component to

atherogenesis and subclinical plaque instability. An increased hs-CRP level is the broadly acknowledged indicator of low-grade systemic inflammation and a cardiovascular disease risk factor, which is independent of CVD.

The role of omega-3 fatty acids in their anti-inflammatory action is to suppress the expression of pro-inflammatory cytokines and induce the nuclear factor kappa-B (NF- kB) a member of transcription factors participating in inflammation. Omega-3 supplementation can also reduce the inflammatory factor of atherosclerosis as it reduces hs-CRP giving cardiovascular event patients with hyperlipidemia an added protective effect.

**5.3 Comparison with the Previous Relation to Omega-3 and Statin Combination Treatment**

This study has satisfactory outcomes in line with previous studies on the efficacy of omega-3 fatty acids and statins efficacy. Research has revealed that even fatty acids omega-3 have the capacity to reduce triglycerides and HDL-C significantly whereas statins majorly influence LDL-C. A major analysis conducted by Cannon et al. (2015) proved that supplementing statin with omega-3 fatty acids resulted in triglyceride levels being reduced further as well as improved cardiovascular outcome. On the same note, the JELIS study (Japan Eicosapentaenoic Acid Lipid Intervention Study) revealed that when omega-3 supplementation was combined with statins, it successfully decreased the amount of cardiovascular events in people who have hyperlipidemia.

This paper adds to the body of evidence that combination therapy can offer viable levels of lipid control and anti-inflammatory activity, making it a potentially viable clinical practice option, especially among those with residual levels of triglycerides in the system despite statin treatment.

**5.4 Clinical Implications and Practicing and Management of the Lipids**

This research study has significant clinical practice implications. Taking into account the fact that triglycerides were considerably decreased, HDL-C was improved, and that omega-3 supplementation has anti-inflammatory effects, clinicians might be interested in combining omega-3 fatty acid supplementation with statins in patients who have not yet gained optimal lipid control with statins alone. This strategy has the potential to potentially maximize lipid management, vascular protection, and reducing residual cardiovascular risk especially among high-risk populations.

The results also indicate that omega-3 fatty acids can be discussed as a part of the extended program of lipid-lowering in case of patients with high triglycerides and low HDL-C as existing methods of treatment might be not sufficient. Depending on results of further trials, current standards of lipid management may need revision to allow the use of omega-3 supplementation in these patients as additional treatment.(10)

**5.5 Limits: Refreshing Length of the Study, the Lack of Long-term Cardiac Statistics, Regional Dietary Variation**

Though the current work offers significant findings, it has a number of limitations that should be reviewed in the further research. One limitation is that the study only lasted 12 weeks, which might not provide all the effects of long term treatment of combination therapy on cardiovascular outcome. Long-term follow-up is needed to evaluate the potential of the changes in lipid profile and layer of inflammation to predict lowered cardiovascular damage in the future.

Further, no hard cardiovascular endpoints were measured in the study including myocardial infarction, stroke, or death. These results are essential in the determination of the clinical importance of the changes witnessed in the levels of the lipids and inflammation. The extent to which combination therapy influences the following endpoints should be evaluated in the future studies.

Lastly, geographical dietary variation may have had to do with the fact that the results were not entirely accurate especially regarding the dietary intake of omega-3. The study was carried on in three countries which had different food habits. Heterogeneity of baseline omega-3 intake may have a potential to affect the outcome of omega-3 supplementation and control should be placed in future studies.

**5.6 FUTURE RESEARCH: Bigger Trials, Effect on Hard Endpoints in Cardiovascular Disease, Dose Response Study**

To further expand on such results, greater scale trials including a wider variety of people would be necessary to confirm the necessity of combination therapy on broad clinical practice. In addition, longer term trials with clinical endpoint outcome measures of hard endpoints like heart attacks and stroke are needed to validate whether the apparent benefit on lipid levels and inflammation is associated with decreased cardiovascular events.

Also the dose-response studies are required to find optimal dosage of omega-3 fatty acids that would reduce triglyceride to the maximum possible and protect the cardiovascular system. The study would give more specific guidelines on the omega-3 supplement when admitted with adverse hypertriglyceridemia when these drugs are used with statins.

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## 6. Conclusion

The research highlighted the fact that combination of omega-3 fatty acids with statin therapy is the safe and effective mode of treatment in case of enduring hypertriglyceridaemia. The combination treatment lowered the levels of serum triglycerides dramatically and ameliorated other vital lipid indicators like HDL-C besides suppressing the excess inflammation as manifested by the lowering of hs-CRP indicators. Notably, the combination treatment achieved the said without creating significant safety issues, a factor that makes it a possible welcome addition to cardiovascular preventive measures. Therefore, this conclusion explains the clinical advantages, safety, as well as how omega-3 supplementation could possibly be incorporated into the existing lipid management.

### 6.1 Omega-3 Fatty Acids as excellent Co-Addition to Statins in the management of Hypertriglyceridemia

The findings presented in this work identify beyond doubt omega-3 fatty acids as a viable addition to statin in treating hypertriglyceridemia. Statistically significant reductions in serum triglycerides were 26.7% in groups of patients who were given omega-3 supplementation (2 g/day) in addition to statins compared to the improvement of just 10.8% in the statin-only group. This considerable decrease in the serum triglyceride level indicates that there indeed may be strong evidence that perhaps omega-3 fatty acids have the capability of reducing triglyceride levels significantly especially among those patients who still have residual hypertriglyceridemia even with statins. Omega-3 fatty acids have been parasitized to decrease triglycerides through an increase activity of enzymes used in lipid metabolism like lipoprotein lipase and a decreased synthesis of VLDL (very-low-density lipoprotein). Together with the use of statins, which mainly affect LDL-C (low-density lipoprotein cholesterol), the addition of omega-3 supplementation is aimed at providing patients with a bigger picture of lipid-lowering protection by simultaneously reducing multiple aspects of the lipid profile.

### 6.2 Lipid Productivity and Inflammatory Marker Modifications With No Serious Safety Concerns

In addition to the noticeable decrease in the triglyceride concentrations, combination therapy caused the enhancement of the HDL-C concentration which is a critical element of a protective lipid profile. The 5.3 percent elevation in the HDL-C values in the combination therapy group implies that omega-3 fatty acids have the potential to improve reverse cholesterol transport, which is a mechanism through which extraneous cholesterol levels get eliminated in the arteries, and atherosclerosis risk is decreased.

Also, combination therapy showed a 21 percent decrease in high-sensitive- C-reactive hard (hs-CRP), a measure of systemic inflammation closely linked with cardiovascular risk. The anti-inflammatory effect of omega-3 fatty acids is necessary to prevent plaque instability and enhance vascular health and can therefore be advantageous in combination with the ceiling effect of statins. Omega-3 addition provides the possibility of covering all the bases by addressing the lipid alterations but also the inflammatory state of hyperlipidemic patients.

There were no major adverse effects in the safety profile of omega-3 supplementation- statin combinations. Mild gastrointestinal complications, also referred to as nausea, bloating, were the most frequently encountered side effects and self-resolved without treatment. Notably, significant safety issues were not of particular concern in this combination therapy like liver toxicity, muscle ache and cardiovascular incidences making it quite tolerable. This is in line with past research findings that showed that omega-3 fatty acids are safe in cardiovascular patients.

### 6.3 Possible Inclusion in Cardiovascular Prevention Plan

Clinical practice implications of the outcomes of this study are considerably dominant in the handling of patients who have resistant hypertriglyceridemia towards the use of statins. Based on the data, it is evident that the addition of omega-3 can be safely used in cardiovascular prevention plans primarily among patients with already high levels of triglycerides who do not adequately respond to statin therapy in isolation. The association between omega-3 fatty acids and statins has the potential to tackle the two issues of lipid abnormality as well as the inflammatory part of atherosclerosis making an overpowering adjuvant in high- EV patients.

The changes in the lipid profile and severe inflammatory markers in the present study endorse the premise that omega-3 fatty acids need to be considered as a routine supplementary therapy to statin medicines in patients with hypertriglyceridemia. The given approach might be especially useful in the group of patients that still have a cardiovascular risk and statins alone might not be effective enough. Implementing omega- 3 supplementation as part of the clinical management of lipids may therefore provide a low risk, well tolerated and effective intervention to lower the burden of cardiovascular disease in a more general clinical population.

Moreover, this research emphasizes the significance of individual treatment approaches to cardiovascular diseases prevention. Patients having high triglycerides levels despite using statins are a population that has high unmet need

and omega-3 supplementation is a chance to fill this gap in treatment. Hence, omega-3 supplementation may become a constituent component of a combined strategy to deal with lipid disorders, together with lifestyle changes, statins, and the rest of medications used to lower lipids.

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## Conflicts of interest

The authors have no conflicts of interest to declare

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