

Should Omega 3 Fish Oils with Statins be First-line Treatment for Patients with
Hypertriglyceridemia?

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death in the United States and hyperlipidemia and hypertriglyceridemia are risk factors for CVD. The current recommendations from the National Lipid Association for primary and secondary prevention is high-, moderate-, or low-statin therapy in combination with lifestyle changes, diet changes, and exercise (Jacobson et al., 2015). This study examines the use of omega3-FAs as a monotherapy or in combination with statin use.

Methods: The study is an integrative literature review using two database searches, PubMed, and Proquest, regarding search words and terms *hyperlipidemia*, *Omega3-FAs*, *hypertriglyceridemia*, *CVD*, and *therapy*. The resulting studies were evaluated with the Critical Appraisal Skills Program (CASP) tool and the Guide to Evidence Hierarchy and synthesized in order to determine a best-practice treatment that optimizes patient outcomes.

Results: 18 trials and articles were reviewed. Recommended treatment options usually included change in lifestyle and diet, but severely elevated levels of LDL, total cholesterol, or triglycerides require immediate medical intervention. Statin use decreases total cholesterol and LDL levels, but has tolerance and drug interaction complications.

Conclusions: Newer forms of omega3-FAs, especially Vasepa, which is a pure form of eicosapentaenoic acid (EPA) with no docosahexaenoic acid (DHA), has shown promise in reducing very low-density lipoprotein (VLDL) levels and slightly decreasing low density lipoproteins (LDL) and is very effective in lowering triglyceride levels. The reduction of these CVD risk factors is vital in optimizing patient outcomes.

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Chapter 1: Introduction

This study addresses the condition of primary treatment for dyslipidemia. Primary care providers (PCPs) have the responsibility of treating patients with dyslipidemia in order to decrease the patients' risk for atherosclerotic cardiovascular disease (ASCVD). Dyslipidemia is a result of high or low levels of blood lipids. Dyslipidemia is assessed using a universal lipid panel blood test that measures total cholesterol (C), high density lipoprotein (HDL), low-density lipoprotein LDL, triglycerides (TG), and sometimes non-HDL-C; these are evaluated according to certain preferred ranges. The US Preventive Services Task Force (2016) defined dyslipidemia as an LDL-C level greater than 130 mg/dl or an HDL-C level less than 40 mg/dl.

Hyperlipidemia and Cardiovascular Disease

Hyperlipidemia is an important health issue because it can lead to ASCVD (Nelson, 2013). This disease process involves plaque from cholesterol deposits building up along the artery walls, leading to atherosclerosis. This buildup of plaque causes a narrowing of the artery walls and limits blood flow, eventually leading to coronary artery disease (CAD). Angina, arrhythmia, heart attacks, and strokes can result if not corrected (Centers for Disease Control [CDC], 2015).

Dyslipidemia and hypertriglyceridemia are recognized bio markers for risk of cardiovascular disease (CVD). CVD is one of the leading causes of death in developed countries (Sasaki et al., 2012). Dyslipidemia and hypertriglyceridemia can affect patients of all ages, including children; however, the most affected population consists of adults over the age of 40 (Kit et al., 2015). Hypertriglyceridemia affects about 25% of the U.S. population (Backes, Anzalone, Hilleman, & Catani, 2016). The National Health and Nutrition Examination Survey

has monitored biomarkers for over 30 years; according to survey data, 31% of the adult U.S. population has elevated triglyceride levels over 150 mg/dl. The report indicates that Hispanic men and women are at the highest risk, followed by Whites-non-Hispanic (Miller et al., 2011).

The CDC (2017) has reported that 78 million Americans have elevated LDL levels. Fewer than half of these people receive treatment for their condition, and people with high LDL-C levels are at twice the risk for CVD. The American Heart Association reported that about 94.6 million adults in the United States, 39.7% of the population, have high cholesterol levels (Benjamin et al.2017). High cholesterol affects every ethnicity within the United States; however, White and Hispanic adults are at higher risk for elevated cholesterol levels than Blacks or Asians (Carrol, Fryar, & Kit, 2015). Dyslipidemia and hypertriglyceridemia are both associated with increased risk of CVD. Thus, HDL, LDL, and triglyceride levels are bio markers for increased risk of CVD.

Neither hyperlipidemia nor hypertriglyceridemia are immediate causes of mortality, but they contribute to ASCVD. According to the National Center for Health Statistics, the number of U.S. adults with diagnosed heart disease is 28.4 million, or 11.7% of the population (Benjamin et al., 2017). The American Heart Association reports that heart disease, including coronary heart disease, hypertension, and stroke, accounts for the greatest cause of death in the United States. Coronary heart disease kills about 360,000 people each year; 790,000 people in the United States have a heart attack with a mortality rate of 14.4% (Benjamin et al., 2017). In the last 90 years CVD has been the leading cause of death in the United States (American Heart Association, 2010).

Statin, niacin, fibrates, and omega-3FAs are standard treatments for risk of CVD due to dyslipidemia (Budhoff, 2016). The PCP has a multitude of choices when deciding upon a prescription regimen; this study is designed to determine a best practice for treating patients at risk for CVD due to dyslipidemia or hypertriglyceridemia—whether with omega-3FAs independently or in combination with other medications.

Cost of Hypertriglyceridemia

CVD results in limited quality of life, chronic chest pain, strokes that can limit movement and independence, and death (CDC, 2015). Patients who survive severe cardiac events such as heart attacks and strokes can have long recovery times, which are physically and emotionally exhausting. Major CVD events change the lives not only of patients, but also of their close family and extended family. It is crucial that PCPs deliver primary and secondary treatment of hypertriglyceridemia as early as possible. Dyslipidemia and hypertriglyceridemia are increasing in patients under 40. The increase in childhood obesity and type-2 diabetes appears to be a possible connection, but that link has not been statistically proven at this point (Miller et al., 2011).

The cost of maintaining lipid levels in recommended ranges is very small compared to the cost of any cardiovascular event. CVD has significant costs to both individuals and society overall. Studies have shown that patients with severe hypertriglyceridemia incur an annual healthcare cost 33% greater than those without the condition (Ito, 2015). The cost to handle a major CVD event runs extremely high and even with insurance, Medicaid, and Medical, the health institution often ends up writing off a large percent of the bill. The annual cost of direct and indirect care for CVD accounted for \$503.2 billion in the United States alone (American

Heart Association, 2010). In 2006 Medicare reimbursement averaged \$10,201 per short-term discharge for cases related to CVD. The medical cost for any treatment of coronary heart disease is expected to grow by 100% between 2013 and 2030 (Benjamin et al., 2017). As these costs continue to grow, not only will patients with CVD incur higher costs, but insurance premiums throughout the nation will rise as insurance companies raise the price of coverage to account for more unhealthy people.

Dyslipidemia and hypertriglyceridemia are controllable risk factors at the primary level of treatment. Patients need to be educated regarding compliance and knowledge of healthy lifestyles. CVD can have a negative impact on work productivity and the economy as a whole. When individuals suffers from a major CVD event, they lose wages during the incident and recovery.

Treatment Options

At this time there are several different pharmacological interventions for dyslipidemia and hypertriglyceridemia, including statins, niacins, fibrates, ezetimibe, bile acid sequestrants, and omega3-FAs (Dixon, Donohoe, Ogbonna, & Barden, 2015). In addition to these medical interventions, education about healthy lifestyle, adherence to a Mediterranean diet, and increased exercise are recommended primary interventions.

Statins are the first line of medical intervention in treating hyperlipidemia as they lowers the risk for ASCVD by reducing total cholesterol and LDL-C and demonstrate pleiotropic and anti-inflammatory effects (Dixon et al., 2015) Statins are in a drug class that inhibit the HMG-CoA reductase enzyme in the liver, which limits cholesterol production overall. The most potent statins are atorvastatin and rosuvastatin and the least potent is fluvastatin. These drugs are

effective at lowering total cholesterol and LDL-C, but they have complications such as hepatic impairment, myalgia, myopathy, rhabdomyolysis, headache, bloating, and diarrhea (Crosta, 2017). Patients with contraindications such as liver disease are not able to take any form of statin medication.

Ezetimibe is a cholesterol absorption inhibitor that lowers LDL-C. This drug is often used in combination with a less potent statin when patients cannot tolerate high-level statins. Niacin is a vitamin B3 that raises HDL-C by decreasing the production of the cholesterol ester transfer protein. Niacin has many safety concerns including facial flushing, increased uric acid levels, glycemic control regulation, and atrial fibrillation. Fibrates lower TG and possibly increase HDL-C. Fibrates and statins have several different contraindications with each other and PCPs should consider all factors for patient outcomes. Bile acid sequestrants work by replacing chloride for bile acid to decrease the amount of bile acid available for cholesterol production. These medications are not well tolerated due to gastrointestinal problems such as diarrhea and flatulence (Dixon et al., 2015).

Omega3-fatty acids (OM3-FAs) are effective at lowering TG levels, possible lowering LDL-C, and raising HDL-C. The OM3-FAs work by reducing the level of triglycerides in the blood through a process of increasing the rate of fatty acid degradation and increasing the clearance rate of TG through the blood system (Mohebi-Nejad & Bikdeli, 2014).

A significant number of recent studies have examined the usefulness of OM3-FAs on the treatment of dyslipidemia. OM3-FAs are categorized into four types: omega-3-acid ethyl esters (Lovaza), icosapent ethyls (Vascepa), omega-3-carboxylic acids (Epanova), and omega-3-acid ethyl esters (Omtryg). Each of these OM3-FAs lowers TG levels, but affects upon LDL-C are

not conclusive (Ito, 2015). One study measured the effects of each type of OM3-FA alone and in combination with a statin in treating dyslipidemia, concluding that the newest form of OM3-FA carboxylic acid (Epanova) was the most potent of the fish oils in lowering triglyceride levels and decreasing LDL-C as well as reducing inflammation and lowering non-HDL-C levels. This study used the ECLIPSE and ECLIPSE-2 trials to achieve their findings (Benes, Bassi, & Davidson, 2016).

Need for Research

These findings provide some insight into the efficacy of omega3-fish oils as a treatment option for dyslipidemia; however, many questions still need answered. First, it is not clear if a combination of statins and OM3-FAs would provide better outcomes for patients versus a monotherapy of either treatment option. Secondly, which OM3-FA is the most effective in treatment as a stand-alone monotherapy or in combination with statins? It is vital that PCPs have answers to these questions as CVD is the leading cause of death in the United States and dyslipidemia and hypertriglyceridemia are major risk factors for CVD.

The American College of Cardiology and the American Heart Association recommend statin as the treatment plan. However, the guidelines of these organizations also mention nonstatin treatment, and it is not clear exactly what this term means. Documenting the benefits of OM3-FAs as a primary treatment may contribute to decreasing the death rate from ASCVD in the United States and reducing the financial burden of ASCVD on individuals and society.

Research Question

To explore this issue, an integrative qualitative review of the literature was conducted. It was designed to address the following research question: Is use of omega 3 fish oils, either alone

or in combination with statins, effective as a first-line treatment for patients with hypertriglyceridemia? The review evaluated research in the medical literature regarding OM3-FAs, statins, dyslipidemia, hypertriglyceridemia, and CVD in an attempt to determine a definitive answer to this question and propose best-practice recommendations for treatment.

This literature review focused on the population of the United States between the ages of 40 and 65 years because hyperlipidemia and hypertriglyceridemia are most common in this age group.

Narrowing the literature review to this population gave the greatest likelihood of yielding actionable results for people who stand to benefit the most from its findings.

Benefits of the Study

This literature review offers several benefits to both patients and primary care providers. The review provides understanding of the effects of treatment options for CVD risk on patients, so patients will benefit from the potential for better patient outcomes. Based on the findings of this review, patients will be able to choose the safest, most effective treatment for lowering their blood lipid levels and therefore decrease their risk for CVD. This literature review examines the benefits of OM3-FAs as a secondary treatment for patients with hypertriglyceridemia in the prevention of ASCVD events.

Additionally, the results of this study can help physicians and other healthcare providers better serve their patients. Currently, there are questions throughout the medical field about what is the best intervention strategy for combatting dyslipidemia and hypertriglyceridemia (Nelson, 2013). This literature review may help resolve these questions by identifying how omega3-FAs may be best used to improve patient conditions. The results may give PCPs more definitive answers for their patients who are facing these diagnoses and want to choose the best treatment

strategy to improve their current health and reduce their risk for cardiovascular disease in the future.

Chapter 2: Review of the Literature

This literature review focuses on determining the most effective treatment for hyperlipidemia and hypertriglyceridemia, whether a monotherapy or a therapy combining statins and omega3-FAs. The primary goal of the review was to determine best practice for a PCP to use to provide the safest and most effective treatment of hyperlipidemia and hypertriglyceridemia. The researcher conducted a systematic literature review to identify current research in regards to omega3-FAs with and without statins in the treatment of hyperlipidemia and hypertriglyceridemia. The literature was examined for evidence-based treatments or valid and reliable controlled trials that would guide the researcher in determining best practice for the PCP.

Literature Review Strategy and Criteria

The literature reviewed was limited to studies published from 2011 to 2017. The only exclusion criterion was non-English language; the initial search required English only articles. Studies conducted outside the United States were permitted as long as the reports were in English. Of the nine studies reviewed, one was from Canada, one was from Spain, one was from Japan, and two were international; the remaining four were from the United States. PubMed and Proquest databases were utilized to conduct the search. Key words and MeSH terms used in the search were *hypertriglyceridemia*, *hyperlipidemia*, *omega3-FAs*, *statins*, *hyperlipidemia*, and *cardiovascular disease*.

Trials that offered strategies for decreasing lipid levels in the high to severe categories were also examined and analyzed to identify possible treatments that might be considered best practice. The researcher used both qualitative and quantitative articles in an attempt to determine

a best practice. The literature included retrospective studies, systematic reviews, narrative analyses, and randomized sample studies, all from peer-reviewed journals. The total number of articles that met the search criteria was 41. After the exclusion criterion of age of subjects between 40 and 65 years was applied, 28 articles remained. The researcher read several of these studies from peer-reviewed journals, but they were not included in the final review if the article repeat sources or findings cite elsewhere. A total of 18 studies were reviewed. Eight are summarized below and their salient features listed in Table 1 at the end of this section. Nine others are summarized in Table 2, also at the end of this section.

The Literature

Bhatt et al. (2017) conducted an international, multi-center, randomized, double-blinded, placebo-controlled, parallel-group trial with 8,179 male and female subjects over 45 years of age; it was known as the REDUCE-IT trial. Patients had to have elevated TG levels and diagnosed cardiac disease to be included. The goal of the trial was to evaluate the effectiveness of a specific omega-3 therapy for reducing cardiovascular events. The trial was ongoing at the time this researcher conducted this review. The preliminary results of this study, published in September 2018, showed a 25% reduction in cardiovascular events. In particular, the omega-3 product Vascepa, when used in conjunction with a statin, proved as effective as atorvastatin for treating hypertriglyceridemia. There are plans to apply to the U.S. Food and Drug Administration for approval of Vascepa to treat hypertriglyceridemia in order to reduce major cardiovascular events. The data and full results from this study will be presented at the annual American Heart Association conference in November 2018 (Hughes, 2018).

The ESPRIT trial was a similar randomized, double-blinded, controlled, parallel-group trial measuring the efficacy of an omega3 free fatty acid (OM3-FFA) used in combination with statin treatment to lower non-HDL-C and TG levels in patients with severe hypertriglyceridemia (Maki et al., 2013). Olive oil was used as a control placebo. One treatment group was provided 2 g/d OO and 2 g/d OM3-FFA, another group was treated with 4 g/d OM3-FFA. The study was 6 weeks long. The results indicate that non-HDL-C levels were reduced in both the 2 g/d (-3.9%) and 4 g/d (-6.9%) groups. TG levels decreased -14.6% and -20.6%, respectively. Very low-density lipoprotein (VLDL) concentration and total cholesterol were reduced in both OM3-FFA groups compared to the control group. This study had a high level of validity based on the lack of bias, consistent findings, and research methods. This results support previously established findings that OM3-FFAs are effective at lowering TG levels in combination with statin therapy in patients with severe hypertriglyceridemia.

Two years after the Maki et al. (2013) trial, Dunbar et al. (2015) performed a sub analysis of the ESPRIT study to determine lipid altering results of Epanova on the reduction of risk of CAD. This was a randomized, double-blinded, controlled study in which participants were administered Epanova (carboxylic acid) in 2 g/d or 4 g/d amounts and compared to a control group of that received olive oil. The researchers found Epanova had a positive effect on several CVD risk factors; it greatly increased LDL particle size and greatly increased VLDL and HDL particle sizes. Elevated Apo CIII is related to elevated risk for CVD events, and the study determined the use of Epanova reduced Apo CIII concentrations. In this study, the OM3-CA therapy, specifically use of Epanova, was performed strictly in combination with statin use; therefore, the results were not able to indicate Epanova's benefits as a monotherapy. The

validity of this study is low to medium as this trial was funded by the pharmaceutical company that developed the therapy tested.

The Kastelein et al. (2014) trial, known as the EVOLVE trial, was conducted worldwide at 74 sites and included 399 patients. This was a double blinded, randomized, parallel, 4-arm study designed to measure the efficacy level of OM3-FA (Epanova), which contains both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Participants were divided randomly into four groups; one received olive oil (OO) as a placebo control, the next received 2 g/d OM3-FA with 2 g/d OO, one received 3 g/d OM3-FA with 1 g/d OO, and the fourth group received 4 g/d OM3-FA. The study was 12 weeks long. Patients were greater than 18 years of age, had TG levels above 500 mg/dl but below 2000 mg/dl. The patients were either untreated for dyslipidemia or had been stable 6 weeks or longer on a statin; all had a BMI equal to or greater than 20. The EVOLVE study had medium level validity based on its low number of participants; nevertheless, its findings were similar to those of other studies. Results showed significant reduction of TG levels and non-HDL-C in all OM3-FA groups. TG levels decreased by 25.9%, 25.5%, and 30.9% with 2, 3, and 4 g/d OM3-FA, respectively, and non-HDL-C was reduced by as much as 9.6% in the 4 g/d OM3-FA group. LDL-C increased in all treatment groups compared to the control group.

A sub analysis of the JELIS study was conducted by Sasaki et al. (2012) to determine if OM3-FA (EPA) reduced the risk of CAD in patients with elevated LDL-C and/or non-HDL-C levels. The researchers attempted to establish non-HDL-C as a risk factor for CAD, a factor that may or may not be indicative of risk for a major CAD event. These researchers were trying to establish the validity of the Kastelein et al. (2014) study, which reported that non-HDL-C and

apolipoprotein B are more closely linked with CAD outcomes than LDL-C. The study, conducted over 5 years with 18,645 patients, was a prospective, randomized, open-label, blinded endpoint study with men and women between 45 and 75 years of age. All patients had TG levels above 250. The researchers reported that patients who failed to meet the LDL-C and/or non-HDL-C goals who were not using EPA were at a significantly higher risk (62%) of CAD events than those who used EPA and also failed to meet the lipid goals. This study has high validity based on its research methods, the size of the study, and the findings. The study confirmed that non-HDL-C levels are positively associated with risk of CAD. The study also confirmed that the use of EPA helped patients meet desired non-HDL-C goals.

Brinton et al. (2013) performed a sub analysis of the ANCHOR study with 702 patients. Their 12-week study was designed to measure the efficacy of a high-purity EPA known as icosapent ethyl (IPE) on reducing TG levels in patients with TG levels between 200 mg/dl and 500 mg/dl. Patients were well established and stable on a statin prescription with LDL-C in the desired range. Seventy-three percent of the test subjects had diabetes mellitus. The researchers administered 2 g/d IPE, 4 g/d IPE, or placebo and measured the effects on lipid serum levels as well as glucose plasma levels. The diabetes patients were categorized based on A1c levels using 6.8 as the median control level. The researchers concluded that patients with diabetes mellitus taking a combination statin and IPE treatment had improved lipid levels; the subjects who received the larger (4 g/d IPE) dose had better results in regards to lowering of TG, non-HDL-C, VLDL, and apolipoprotein B (Apo B). IPE treatment did not alter glycolic management of patients with diabetes mellitus. The study had a low level of validity as it was a post hoc

analysis and the authors were provided grant support by the pharmaceutical company Amarin Pharma, Inc.

The Laidlaw, Cockerline, and Rowe (2014) study was an open-label, randomized, cross-over study designed to test blood serum levels in 35 patients using four different sources of fish oil omega3-FAs: krill, salmon, EE fish, and rTg fish. The trial consisted of 28-day cycles on each omega3 source with a 4-week washout period between cycles; all participant completed every source. The rTG fish oil provided the best CVD risk reduction and greatest EPA increase in blood serum. Krill and salmon were the least effective. Limitations of the trial include small sample size and lack of specific blood lipid panel counts. The authors were independent from any pharmacology company and worked as independent researchers.

In a single-blinded, parallel-group, randomized, controlled trial, Garcia-Hernandez et al. (2013) examined how oxidation affects OM3-FA (EPA and DHA) efficacy in women. The 52 participants were placed in one of three groups to receive three different substances: highly oxidized capsules, less oxidized capsules, or no capsules. Participants in each group had a fish-rich diet. Glucose, triglycerides, and total cholesterol were measured for each group after 30 days. The findings showed the less oxidized capsules provided the greatest decrease in TG levels and total cholesterol and were therefore the most effective. The more oxidized capsules had a greater negative effect on lipid levels than a fish-only diet. These findings are important in showing that nonprescription dietary OM3-FA supplements can have adverse effects on lipid levels. The study was limited by its small sample and the fact that it was done in a single location in Spain.

Synthesis of the Literature

This literature review demonstrated that statin use is the primary treatment for reducing risk of CVD due to high and severe LDL-C levels. The research analyzed suggested that statin use is not always effective at reaching TG and non-HDL-C target goals. Omega3-FAs help lower these particular lipid levels. Some of the trials have raised questions as to whether non-HDL-C may be a better predictor of ASCVD events. Several of the studies identified VLDL and APO B and Apo CIII as predictors of ASCVD events. The use of high-dose EPA was shown to reduce the risk of CVD by 25% in patients who maintained TG levels over 150 even with prescription regimen. All of the studies confirm that omega3-FAs are beneficial in lowering TG, non-HDL-C, VLDL, and Apo B and CIII. Omega3-FAs are well tolerated, have no drug-to-drug interactions, and have no pancreatic or liver effects.

All of these studies bring us back to the important question of whether omega3-FA treatment might be the best practice for a PCP in treating hyperlipidemia and/or hypertriglyceridemia. Clearly the studies show a beneficial effect, but the question remains: Can omega3-FAs provide a monotherapy without the risk factors associated with statins, fibrates, and niacins? The newer OM3-FAs (EPA, carboxylic acids) show possibility as a primary treatment. However, any attempt to discover a single best practice must be made based on the best available data and research. This project was designed to provide this important information.

Table 1

Selected Features of Nine Studies Reviewed

Author (Year Published) Country	Variables DV IV	Study Design	Sample Size	Sample Characteristics	Methods	Results	Conclusions, limitations. Level of Evidence
Bhatt et al. (2017) Worldwide	DV: Reduction of CV events IV: omega- 3 therapy	Trial	7,790 patients	Men and women > age 45 with elevated TG levels and diagnosed cardiac disease	Randomized, double-blind, placebo- controlled, parallel-group trial	Phase 3b, international, multi-center, placebo- controlled, parallel- group trial.	The study has not ended; preliminary finding: omega- 3 FAs combined with statins in patients with elevated TG levels reduces CV events. Level I
Maki et al. (2013) U.S.	DV: non- HDL-C and TG levels IV: addition of OM3- FFA to statin therapy	Trial	647 subjects	TG levels \geq 200 mg/dL and <500 mg/dL, high risk of CVD	Participants randomly placed into one of two treatment groups or control group	Subjects receiving 2 g/d and 4/gd OM3-FAA showed significant reductions in TG levels, non-HDL-C, LDL-C rose significantly in the 2 g/d, but not the 4 g/d test group.	Statin in combination therapy with OM3-FAA is effective in lowering TG levels. Limitation: researchers paid by the company that created the OM3-FAA used in the study. Level II
Dunbar et al. (2015) U.S.	DV: CAD risk reduction IV: OM3- FA Epanova	Trial	647 patients 96 research sites.	Mostly non- Hispanic White men and women, treated with statin but with TG levels 200- 500 mg/dl	Randomized, controlled, double-blind study	OM3-CA treatment reduced TG levels, increased LDL particle size, decreased VLDL and HDL particle size.	OM3-CA associated with changes in lipoprotein size and concentrations. APO CIII reductions significant in patients with >200 mg/dl but < 500 mg/dl. Level II
Kastelein et al.	DV: non- HDL-C and	Trial	399 subjects,	Men and women >18 yrs	Double-blind, randomized,	The use of OM3-FAA Epanova is effective at	THE OM3-FAA Epanova reduces severe TG levels but

(2014) Multinationa l	TG levels IV: therapy with investigatio nal OM3- FFA (Epanova)		74 clinical sites	of age, TG levels >500 mg/dl but < 2000 mg/dl. Untreated for dyslipidemia or stable on a statin regimen > 6 weeks, BMI ≥ 20.	parallel, 4-arm study using placebo, 2 g/d, 3 g/d, and 4 g/d sub groups.	lowering TG levels in patients with severe hypertriglyceridemia.	increases LDL-C levels. Limitation: researchers are employees of Epanova drug- producing company. Level II
Sasaki et al. (2012) Japan	DV: CAD and Non- HDL-C level IV: EPA omega-3 FA therapy	Prospec tive, random ized, open- label, blinded - endpoi nt evaluati on trial	18,645 patients	Men 45-75 years of age and post menopausal women under age 75 years, TC levels >250	Subjects randomly assigned to receive statin alone treatment or statin in combination with EPA	Reduction of LDL-C also reduces the risk for CAD; EPA treatment reduced risk of CAD in patients with dyslipidemia.	EPA may be effective in reducing risk of CAD in patients who do not improve their LDL-C or non- HDL-C serum levels with or without statin use. Limitation: conducted only in Japan. Level II
Brinton et al. (2013) U.S.	DV: Lipid & inflammato ry parameters in patients with diabetes IV: Icosapant ethyl (IPE)	Post hoc subgrou p analysis of ANCHO R study, double- blind, random	702 patients	Patients with diabetes mellitus > 18 yrs of age, fasting TG levels > 200mg/dl-500 mg/dl	Median placebo- adjusted % change from baseline to week 12 in fasting TG levels	Patients receiving IPE in combination with statin decreased TG levels by ≥ 20%, improved VLDL-TG and hsCRP.	IPE 4 g/d with statins significantly improves lipid and lipoprotein and inflammatory parameters without worsening LDL-C or glycemic control. Limitations: sponsorship of research from pharmacology sources. Level II

		ized					
Laidlaw, Cockerline, & Rowe (2014) Canada	DV: Serum lipid levels and CVD risk reduction IV: omega-3 FAs from 4 different source	open-label, randomized, cross-over	35 hypercholesterolemic patients treated with statins	>18 yrs of age, pancreatic carcinoma, life expectancy >3months, tumor associated weight loss>5%, Karnofsky score>60%, no allergy to seafood, oral nutrition, and no blood	Subjects received four types of omega3 FAs, each for 28 days with a 4-week wash out period between, blood serum levels were measured after each 28-day cycle.	Absorption rate, in order: rTG fish oil, EE fish oil, Triglyceride TG salmon oil, PL krill oil. The rTG oil provided the greatest increase in CVD risk reduction factors.	Omega3-FAs reduce risk for CVD overall, but type and dosage affects efficacy. Limitations: small sample size and lipid panels not utilized to provide lipid altering effects. Level II
Garcia-Hernandez et al. (2013) Spain	DV: Glucose, cholesterol, TG, and GPT levels. IV: Oxidation of fish oil capsules	Single-blind, parallel-group, randomized controlled trial	52	Female aged 25-75. All had dyslipidemia with no current drug treatment. Cholesterol level 250-300 mg/dl, TG level 160-175 mg/dl.	Women randomly assigned to one of three test groups: one receiving two capsules daily of less oxidized 300 mg EPA + DHA, a second group received two capsules of a more oxidized 300 mg EPA +	Cholesterol and TG levels decreased in all groups, the group with the less oxidized capsules gained the greatest decrease in serum-level TG.	Diet alone is not enough to reduce TG and cholesterol levels to recommended levels once dyslipidemia exists. Omega3-FAs are needed in greater amts. Than than 300 mg daily. Oxidation affects efficacy of omega3-FAs and most companies add Vitamin E, A, or D to dietary supplements, increasing oxidation. Limitation: small sample size, and nonprescription strength omega3-FAs. Level II

					DHA, the third group had diet alone.		
Brinton & Mason (2017) U.S.	DV: lowering of TG levels and non-HDL-C levels IV: Omega-3 FA	Integrated literature review	23 meta-analysis, systematic reviews	Studies of patients with dyslipidemia and/or hypertriglyceridemia who received some form of omega-3 FA regimen	Examination of data pertaining to omega-3 FAs, hypertriglyceridemia, dyslipidemia, and statin combination therapy.	All prescription omega-3 FAs are effective in lowering severe triglyceride levels, EPA improves triglyceride levels without increasing LDL-C levels.	The use of omega-3 as a secondary treatment is still undergoing evaluation. EPA appears to lower TG levels without raising LDL=C levels unlike DHA containing omega-3 FAs. Level II

Table 2

Comparison of Themes in Literature Reviewed

Author, year, Location	Type of Omega-3	Combination therapy or monotherapy	Results/findings	Indications for treatment	Indications for further research
Backes, Anzalone, Hilleman, & Catini 2016 United States	OM3EE, OM3FA, EPA, DHA, IPE, EPA EE, OM3CA, Dietary supplement FAs	Combination statin+OM3EE Statin+OM3CA Statin+IPE	All forms of OM3-FAs lower TG levels both in combination of statin therapy and as a monotherapy.	Severe TG levels can be reduced with OM3-FAs, lowering TG levels reduces risk of CVD	LDL-C to nonHDL-C levels as risk factors for CVD, Level V
Benes et al, 2016 United States	OM3-CA (Epanova)	Both in combination with statin and as a monotherapy	OM3-CA has greater bioavailability than older forms of OM3-EE	Patients with >500 mg/dl TG levels are effectively treated with OM3-CA, statins do not work for all patients.	LDL particle size, nonHDL levels and monotherapy using OM3-CA Level V
Kedia & Lynch, 2015 United States	Lovaza, Vascepa	In combination with statin	Vascepa proved more effective at lowering TG serum levels as well as decreasing tot C, LDL-C, and non HDL-C.	Statin therapy does not meet every patient's needs, elevated TG levels may be decreased with Vascepa	Vascepa provides greater efficacy than other forms of OM3-FAs. Level VI
Ito, M. 2015 United States	Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), Lovaza, Epanova, Vascepa	Both in combination of statin and as a monotherapy	All OM3-FAs are effective at lowering TG levels and similar in results.	Elevated TG can be treated with any OM3-FA, inflammation, lipid size, and thrombosis effects.	Actual long-term trials to prove reduced CV events using OM3-FA's. Level VI

Kim & McCormack, 2014 New Zealand	Purified EPA (Vascepa)	monotherapy	This purified EPA known as icosapent ethyl acid (IPA) is proven to lower TG without raising LDL-C.	Severe TG levels cause pancreatitis and increased risk for CV events.	Ongoing trials to measure efficacy of IPA in reducing a first-time CV event. Level VI
Blair & Dhillon, 2014 New Zealand	OM3-CA (Epanova)	monotherapy	4 g/d OM3-CA reduce TG levels, total cholesterol, VLDL-C, and Apo-CIII levels.	Severe hypertriglyceridemia treatment should be OM3-CA	OM3-CA trials compared to IPA for best patient results regarding all lipid serum levels. Level V
De Lorgeril, Salen, Defaye, & Rabaeus 2013 France	OM3-FA- EPA and DHA	Comparison between monotherapy and combination therapy with statin	Statin and OM3-FAs in combination appear to reduce the benefits.	Patients with statin use may not benefit from OM3-FA treatment especially reducing CVD risk.	Statin use may not be most productive when considering medical effects Level V
Minihane, 2013 England	EPA, DHA	In combination with statin or monotherapy	EPA and DHA lower TG levels, OM3-FAs have cardioprotective benefits.	Hypertriglyceridemia treatment, counteracting dyslipidemia associated with obesity and T2DM.	Long-term studies establishing OM3-FA reduction in CVD events. Level VII
MacMahon, & Wierzbicki, 2011 England	OM3-FAs	In combination with statins and as a monotherapy	EPA and/or DHA reduce inflammation and reduce TG levels.	OM3-FAs reduce risk of CV events.	Long-term studies establishing CVD event reduction. Level III

Chapter 3: Methods

This study utilized an integrative review approach to search for, gather, and synthesize qualitative and quantitative data pertaining to the use of omega3-FAs to treat hypertriglyceridemia and hyperlipidemia either as a monotherapy or in combination therapy with statins. The researcher used the suggested outline recommended by Whittemore and Knafl (2005) as the most effective format for synthesizing qualitative and quantitative data. This approach was chosen as it allowed the researcher to draw from a variety of different types of articles, studies, and research; in fact, the integrative review is the only strategy that does this. The Whittemore and Knafl model incorporates problem identification, literature search, data evaluation, and data extraction and analysis.

Problem Identification

Over the last 40 years the association between hyperlipidemia and hypertriglyceridemia and the risk of ASCVD has been well established. However, the best treatment for these conditions when multiple-level lipid discrepancies exist is not clear. Severe LDL-C levels are usually treated with a statin as an immediate response to lower the risk of heart attack or stroke (US Preventive Services Task Force, 2016). Omega3-FAs are often used to lower triglyceride levels both in combination with statins and as a monotherapy. The newer forms of omega3-FAs have higher concentrations of EPA without the DHA. DHA has been shown to elevate LDL-C, a fact that has caused concern among PCPs. The newer forms of omega3-FAs may provide a more effective treatment with fewer drug interactions as well as fewer side effects (Kim & McCormack, 2014). The purpose of this integrative review was to research the best treatment for patients with hyperlipidemia and hypertriglyceridemia in order to prevent CVD.

Literature Search

Three different databases were searched for relevant sources; however, the researcher deemed data older than 2011 would not provide any new insight into the research question. All research was conducted over the internet using PubMed and ProQuest databases. The following MeSH terms were used: *treatment of hypertriglyceridemia*, *treatment of hyperlipidemia*, and *benefits of OM3-FAs*; subsearch terms were *monotherapy*, *combination therapy*, *lipid levels*, and *cardiovascular risk factors*.

Research studies were searched, analyzed, and synthesized if they study pertained to the research topic. An ancestry search was used in several situations. The clinical trials were evaluated separately from other articles such as systemic reviews and qualitative and quantitative studies. Articles were evaluated for peer review and valid findings. The researcher analyzed all data looking for patterns, recommended treatments, similar findings, and, most importantly, new findings. The results were used to answer the research question: Is use of omega 3 fish oils, either alone or in combination with statins, effective as a first-line treatment for patients with hypertriglyceridemia? No ethical approval from an IRB was necessary for this study as this was an integrative literature review. No individual patient information was used, so consent was not required. This project required the researcher and a committee consisting of a faculty advisor, a mentor, and a content expert. The Fresno Pacific University librarians were utilized as needed.

Data Evaluation

For this integrative qualitative project, the CASP literature appraisal tool was used to determine the value of each study. Only those studies that demonstrated validity, reliability, and minimal bias were used in the study. The Quick Guide to an Evidence Hierarchy of Designs for Cause-Probing Questions was utilized to measure validity and reliability (Leung, 2015). Use of

the CASP tools for randomized controlled trials and quantitative studies ensured the researcher determined rigor and appropriateness for inclusion in this integrative, qualitative study. The researcher did not exclude material based on the evaluation tools, but the information was considered during the analysis part of literature.

Data Extraction and Analysis

Studies were placed in a literature review matrix (Table 1). The matrix gave a summary of methods, results, and conclusions of the studies reviewed. In addition, the researcher utilized another matrix comparing and contrasting the resulting conclusions in order to classify themes and patterns (Table 2). Results were analyzed for concepts, uses, and best practices. The researcher synthesized all findings relevant to the research question and applicability in reducing the risk of CVD. Gaps in information were determined and shared and recommendations were made. This literature search process is illustrated in Figure 1.

Chart 1

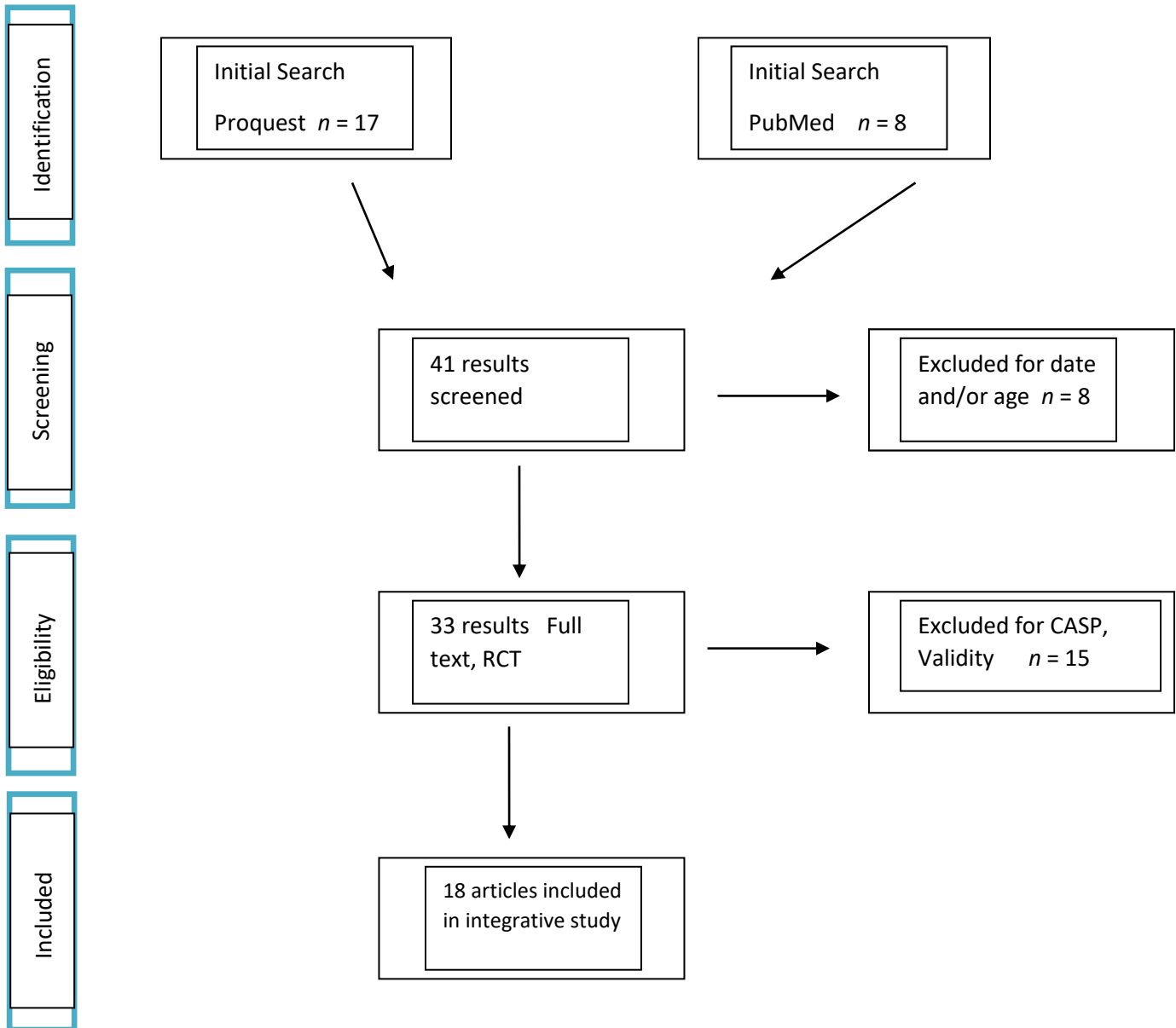


Figure 1. Literature search process.

Chapter 4: Results

This researcher reviewed a total of nine trials and nine articles in this study. The overall research from all 18 sources shows consistent findings regarding lipid levels having a direct predictive relationship to ASCVD. The research does not agree on which lipid level is the best indicator as a stand-alone factor, but non-HDL-C, LDL-C, Apo B, and Apo CIII have the highest correlations as predictors of a major CVD event. Every finding conclusively show all forms of omega3-FAs reduce TG levels both in combination with a statin or as a monotherapy. There are consistent findings that demonstrate omega3-FAs are effective at reducing TG and non-HDL-C levels and increasing HDL-C levels, particularly EPA and carboxylic acids, the newer forms of omega3-FAs.

An important finding for all providers to make note of is that the level of oxidation within the omega3-FA has a direct correlation to its effectiveness; therefore, pharmaceutical-grade OM3-FAs are the only recommended treatment. Patients with diabetes mellitus with a statin and IPE treatment of 4g/d had the best improvement in lowering TG, non-HDL-C, VLDL, and Apo B levels while having no impact on blood glucose. Epanova consistently demonstrated the benefit of reducing CVD events by increasing LDL particle size and reducing particle size of both VLDL and HDL. There are significant indicators that the use of EPA to lower non-HDL-C provides a substantial decrease in the risk of CAD. Epanova reduces TG levels by up to 30.9% and non-HDL-C levels by up to 9.6%.

The studies demonstrated that OM3-FAs are effective in lowering TG and non-HDL-C levels both in combination with a statin and as a monotherapy. There is no evidence that omega3-FAs are effective in reducing total cholesterol levels. Omega3-FAs are effective in

reducing CVD risk factors of VLDL and HDL particle size and TG, non-HDL-C, VLDL, and Apo B levels.

Chapter 5: Discussion

Dyslipidemia and hypertriglyceridemia are recognized indicators of risk for ASCVD. CVD is the leading cause of death in the United States. About 360,000 deaths occur every year in the United States from coronary heart disease. PCPs are the first level of intervention and education to help patients control dyslipidemia early, before CVD onset. At the time of this literature review, a patient presenting with very high levels of total cholesterol often receives a statin as first-line treatment. Statins are often not well tolerated, have contraindications, and can cause liver problems. The use of OM3-FAs would provide patients with a treatment with fewer side effects, lower risk of medicine interactions, and much better tolerance. OM3-FAs are generally prescribed in combination with statins if total cholesterol and TG levels are greater than 500. This combination therapy was based on the two earlier forms of OM3-FA, which contained DHA. EPA and carboxylic acids are the newest forms of OM3-FA; exploring their use as a monotherapy or in combination with a statin as a first-line treatment for preventing and/or controlling CVD was the purpose of this literature review.

Key Findings

The purpose of this literature review was to determine if OM3-FAs should be considered as first-line treatment for patients over 40 years of age with hypertriglyceridemia. The findings were consistent, showing similar results and conclusions across the 18 studies reviewed; only minor differences were seen, based upon the specific type of OM3-FA used in the study. The Bhatt et al. (2017) and Maki et al. (2013) studies showed significant benefits from using OM3-FAs in combination of a statin to reduce TG levels and non-HDL-C levels in order to reduce the risk of a major ASCVD event. The Kastelein et al. (2014) trial demonstrated that OM3-FAs were effective at lowering both TG levels and non HDL-C levels. Participants in these tests

showed consistent results whether using OM3-FAs as a monotherapy or in combination with a statin. This findings suggest that non-HDL-C is a better indicator of a CVD event than LDL-C levels.

The Sasaki et al. (2012) trials demonstrated that the use of EPA helps patients achieve recommended non-HDL-C levels and, in fact, reduces the risk of a major CVD event by 62%. Results of this study indicates that non-HDL-C and Apo B levels are more indicative of a potential ASCVD event than LDL-C levels. The Dunbar et al. (2015) trial demonstrated the use of carboxylic acid to reduce the risk of CAD. The study reported that Epanova is an effective treatment for lowering non-HDL-C levels. Epanova greatly increases the size of LDL particles, allowing for better metabolism, and significantly reduces VLDL and HDL particle size. The Epanova therapy in the Dunbar et al. study was given in combination with statins.

What the Results Mean

CVD is the primary cause of death in the United States. Hyperlipidemia and hypertriglyceridemia are correlated to the risk of a major ASCVD event. PCPs use statins as a first-line treatment for high-risk total cholesterol in an effort to prevent or manage CAD. OM3-FAs are often used when hypertriglyceridemia above 500 is also presented. LDL-C level is used by PCPs to predict risk of a major CVD event. This review suggests non-HDL-C, VLDL, and APO-B levels are more indicative of major CVD events, especially as many heart attacks, strokes, angina, and arrhythmias occur when LDL-C levels are not abnormal. The PCP has the responsibility of educating and treating patients with dyslipidemia to help them manage the condition, maintain good health, prevent ASCVD, and enjoy the highest quality of life possible. A major CVD event is life altering for both patients and their family members in many ways

other than just the event; it affects financial health, daily activities of life, careers, lifestyle, and physical and mental health.

This literature review was conducted to determine the best first-line treatment for hyperlipidemia, whether a statin, a combination of statins and OM3-FAs, or OM3-FAs as a stand-alone treatment. The results indicate that there is no single best first-line treatment that covers hyperlipidemia as a single best prescriptive means; rather each individual case requires in-depth consideration of the full lipid panel, lifestyle, diet, and presenting health issues. This literature review has demonstrated the effectiveness of OM3-FAs, especially the newer forms of EPA and carboxylic acid, in reducing non-HDL-C, Apo-B, and TG levels, which appear to be more reliable as indicators for a major ASCVD event. This review could not determine if the best treatment is as a combination therapy or if using OM3-FAs as a stand-alone treatment is more beneficial. There was support for both cases, but if lowering total cholesterol levels is a goal, then the statin combination treatment appears to work the best. It is important for every PCP to understand that statin treatment alone often is not well tolerated, is ineffective at lowering TG levels, and does not lower non-HDL-C levels as well as when combined with the newer OM3-FAs.

Implications for Practice, Education, Policy, and Research

This literature review has direct implications for advanced practice nurses as PCPs. The role of the advanced practice nurse is to provide the best treatment that will return a patient to health and/or maintain health. Dyslipidemia, especially hyperlipidemia and hypertriglyceridemia, are direct risk factors for CAD and possible future CAD major events. This review strongly suggests that although total cholesterol and LDL-C levels are indicative of possible ASCVD events, TG levels and non-HDL-C levels are more reliable indicators of

ASCVD. OM3-FAs are effective at lowering TG and non-HDL-C levels. OM3-FAs help lower Apo B and VLDL. The advanced practice nurse must educate patients on a case-by-case basis about diet, exercise, and lifestyle in order to reduce hyperlipidemia. It is also up to the advanced practice nurse as the PCP to prescribe medication that will help patients meet desired lipid levels. Statin use may be required if cholesterol levels so indicate, but a medical-grade OM3-FA prescription may be adequate in many situations, either as a monotherapy or in combination with a statin.

This literature review has implications for advanced practice nurse education. The curriculum for the advanced practice nurse in treating hyperlipidemia covers statins, fibrates, and OM3-FAs. No change is necessary, but there should be a concentrated effort to teach the advanced practice nurse every option and the side effects and contraindications for each type of medicine.

This literature review has implications for policy regarding treating dyslipidemia with the best and most appropriate medication regimen. Statins are usually effective forms of treatment, but with hepatic risk, side effects, non-tolerance, and contraindications with many other types of drugs, the use of OM3-FAs should be considered when appropriate. As the research showed, non-pharmaceutical-grade OM3-FAs are not as effective and in fact many have little effect, so it is imperative that pharmaceutical-grade OM3-FAs become acceptable treatment regimens within both health agencies and insurance companies.

This literature review encourages more specific research regarding OM3-FAs as stand-alone treatment in reducing the risk of major ASCVD events. It would be beneficial if patients on a stand-alone treatment of OM3-FAs over a 10-year period could be shown to have a

substantially significant reduction of ASCVD events. This sample could be compared to patients with combination therapies.

Limitations

This integrative literature review was approached with an open mind and nothing more than interest regarding the effectiveness of newer-generation OM3-FAs in improving hyperlipidemia. There is a risk of bias in the findings as several of the studies were financed or conducted by pharmaceutical companies that created the OM3-FAs they studied. However, those findings were confirmed through independent research studies conducted by researchers with no affiliation to a drug company.

Another limitation of this study is the lack of research on the omega 3 fish oils, EPA (Vascepa). Although the few studies available have some promising findings, they are inconclusive due to small sample sizes; thus the need for further research of these therapies.

The reliability and validity instruments used in this study ensured personal bias was not a factor. Sample sizes of the trials also led to reliability and validity regarding the findings of this study.

Conclusion

This researcher will be an advanced practice nurse with the responsibility of helping patients prevent CAD, especially major ASCVD events. Hyperlipidemia is a recognized risk factor for CAD. The American Heart Association reported that 94 million Americans, approximately 40% of the population, have some form of dyslipidemia (Benjamin et al., 2017). Statins are effective in lowering total cholesterol and usually lowering LDL-C levels, but they have contraindications and hepatic risks. This literature review showed that the newer EPA and carboxylic acid OM3-FAs reduce non-HDL-C, Apo B, and VLDL levels. These three lipid

levels are direct risk indicators for a major CVD event. OM3-FAs are well tolerated, have little to no medicine-to-medicine interactions, and have very low side effects.

This literature review was conducted to determine if use of omega 3 fish oils with statins would be effective as a first-line treatment for patients with hypertriglyceridemia. The REDUCE-IT study, whose findings were just published in September 2018, indicates a 25% reduction in CVD events with OM3-FA therapy. Helping patients maintain their health and avoid life-altering CVD major events is the responsibility of the advanced practice nurse. OM3-FAs have a clear role in our efforts in certain cases, as this literature review has demonstrated. There is still a need for further research regarding improved patient health for patients with hypertriglyceridemia, especially those with TG levels between 200 and 499.

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Introduction

Almost 32% of the U.S. population is at risk for cardiovascular disease due to dyslipidemia. The most common forms of dyslipidemia include hyperlipidemia and hypertriglyceridemia (CDC, 2015). The FNP as a PCP is in the best position to provide primary treatment in order to prevent CVD.

Problem Identification

The main reason why hyperlipidemia is a problem is because it can lead to cardiovascular disease (Nelson, 2013). Specifically, it leads to atherosclerosis, which is a process in which plaque, that is comprised of cholesterol deposits, build up along the walls of the arteries causing blockage. Ultimately, it can cause coronary artery disease, which can have symptoms including angina and arrhythmia. Ultimately, a blockage of the artery can trigger a heart attack or stroke ("Coronary Artery Disease," 2015).

Literature Search

To answer this question, an integrative qualitative review of literature will be conducted. The literature reviewed was limited to studies from 2011 to 2017. The only exclusion criterion was non-English language; the initial search had already required English only for review.

Studies conducted outside the United States were permitted as long as the reports were in English. Of the 9 trials reviewed, 1 was from Canada, 1 was from Spain, 1 was from Japan, and 2 were international; all the other studies were from the United States. PubMed, CINAHL, and ProQuest databases were utilized to conduct the search

Data Evaluation

The researcher used both qualitative and quantitative articles in an attempt to determine a best practice for this project. The literature included retrospective studies, systematic reviews, narrative analysis, randomized sample studies from peer reviewed journals. The total number of articles was 41. After exclusion criteria of age of subjects between 40 -65 there were 28 articles. The researcher read several of the peer reviewed articles, but they were not included in the findings if they were not focused on the original research question.

Data Analysis

For this integrative qualitative project the CASP Literature Appraisal Tool will be used to determine the value of each study. Only those studies that demonstrate validity, reliability, and minimal bias will be used in this study.

The researcher will synthesize all findings relevant to the research question and applicability in reducing the risk of CVD. Gaps in information will be determined, shared and recommendations will be made.



Presentation/Results

After analyzing and synthesizing all available research, the data demonstrates a clear reduction of major adverse cardiac events (MACE) by 25% when EPA is used in conjunction with statin treatment. Omega3-FA's reduce LDL, VLDL, and APO B lipid levels (Amarin Corporation, 2018). The reduction of these lipids have significant clinical indications as a risk for cardiovascular disease. The use of 4g/day has been proven to provide lower risk of MACE and would benefit patients who are not responding with desired triglyceride levels while treated with statin therapy.

References

Available upon request