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Review

Update on marine omega-3 fatty acids: Management of dyslipidemia and current omega-3 treatment options

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) is currently the primary target in the management of dyslipidemia, and statins are first-line pharmacologic interventions. Adjunct therapy such as niacins, fibrates, bile acid sequestrants, or cholesterol absorption inhibitors may be considered to help reduce cardiovascular risk. This review discusses the need for alternative adjunct treatment options and the potential place for omega-3 fatty acids as such. The cardiovascular benefits of fish consumption are attributed to the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and a variety of omega-3 fatty acid products are available with varied amounts of EPA and DHA. The product types include prescription drugs, food supplements, and medical foods sourced from fish, krill, algal and plant oils or purified from these oils. Two prescription omega-3 fatty acids are currently available, omega-3 fatty acid ethyl esters (contains both EPA and DHA ethyl esters), and icosapent ethyl (IPE; contains high-purity EPA ethyl ester). A pharmaceutical containing free fatty acid forms of omega-3 is currently in development. Omega-3 fatty acid formulations containing EPA and DHA have been shown to increase LDL-C levels while IPE has been shown to lower triglyceride levels without raising LDL-C levels, alone or in combination with statin therapy. In addition, recent studies have not been able to demonstrate reduced cardiovascular risk following treatment with fibrates, niacins, cholesterol absorption inhibitors, or omega-3 fatty acid formulations containing both EPA and DHA in statin-treated patients; thus, there remains a need for further cardiovascular outcomes studies for adjunct therapy.

Contents

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Abbreviations

ACCORD Action to Control Cardiovascular Risk in Diabetes
AHA American Heart Association
AIM-HIGH Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes;
ALA alpha linoleic acid;
Apo B apolipoprotein B;
CHD coronary heart disease;
CI confidence interval;
COMBOS Combination of Prescription Omega-3 with Simvastatin study;
CV cardiovascular;
DHA docosahexaenoic acid;
ECLIPSE Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation;
ENHANCE Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial;
EPA eicosapentaenoic acid;
ESPRIT Efficacy and Safety of Add-on Epanova to Statin in Subjects With Persistent Hypertriglyceridemia and High Risk for Cardiovascular Disease study;
EVOLVE Epanova for Lowering Very High Triglycerides study;
FIELD Fenofibrate Intervention and Event Lowering in Diabetes;
GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca;
GISSI-HF Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure;
HDL-C high-density lipoprotein cholesterol
HPS2-THRIVE Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events;
HR hazard ratio;
IPE icosapent ethyl;
IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial;
JELIS Japanese EPA Lipid Intervention Study;
LDL-C low-density lipoprotein cholesterol;
Lp-PLA_2 lipoprotein-associated phospholipase A_2;
MARINE Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week study with an Open-label Extension;
NHANES National Health and Nutrition Examination Survey;
NKO Neptune Krill Oil;
OM3EE omega-3 acid ethyl esters;
OMEGA Omega 3 Fatty Acids on Top of Modern Guideline-adjusted Therapy;
OM3FFA omega-3 free fatty acids;
OPERA Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation trial;
ORIGIN Outcome Reduction with Initial Glargine Intervention;
PUFA polyunsaturated fatty acid
REDUCE-IT Reduction in Cardiovascular Events with EPA-Intervention Trial;
T2DM type 2 diabetes mellitus;
TC total cholesterol;
TG triglycerides;
TRIFECTA Trial for Efficacy of CaPre on Hypertriglyceridemia;
US FDA United States Food and Drug Administration;
VA-HIT Veterans Affairs High-density Lipoprotein Intervention Trial;
VLDL-C very-low-density lipoprotein cholesterol;
VLDL-TG very-low-density lipoprotein triglycerides.

1. Introduction

The relationship between low-density lipoprotein cholesterol (LDL-C) levels and the risk of coronary heart disease (CHD) in a broad patient population was firmly established by landmark studies conducted in the 1980s [1–4]. As a result of widespread adoption of strategies to lower LDL-C levels over the ensuing three decades, including the development of statins, mean LDL-C levels have declined in the United States [5]. Atherogenic dyslipidemia is characterized by elevated triglycerides (TG) and small LDL particles with reduced levels of high-density lipoprotein cholesterol (HDL-C) and often elevated apolipoprotein B (Apo B) and non-HDL-C [6,7]. While LDL-C levels have declined, results from the National Health and Nutrition Examination Survey (NHANES) showed that 31% of US adults have high fasting TG levels (≥150 mg/dL [1.70 mmol/L]), 16% have high TG levels (≥200 mg/dL; 2.26 mmol/L), and 1% have very high TG levels (≥500 mg/dL; 5.65 mmol/L) [8,9]. Substantial progress has been made in the last decade in understanding the effects of omega-3 fatty acids on cardiovascular (CV) disease [10] and lipid parameters including TG and LDL-C [11,12]. The purpose of this review is to provide an update on omega-3 fatty acid treatment options for patients with dyslipidemia.

2. Management of dyslipidemia: guidelines and treatment options

LDL-C remains the primary target for lipid-lowering therapy in the management of dyslipidemia [6,13]. Current recommendations specify that the LDL-C goal is <100 mg/dL (2.59 mmol/L) for high-risk patients (CHD or CHD equivalents, including those with diabetes; 10-year risk >20%) and <70 mg/dL (1.81 mmol/L) for very-high-risk patients (multiple major risk factors, severe and poorly controlled risk factors, multiple risk factors of the metabolic syndrome and acute coronary syndrome) [13]. Non-HDL-C is the secondary target in patients with TG ≥ 200 mg/dL (5.18 mmol/L) [6]. Therapeutic lifestyle changes are an essential first-line modality for clinical management of dyslipidemia in all patients [6,13]. For individuals who cannot attain target LDL-C levels with diet and exercise alone, statins are first-line pharmacotherapy [6]. In patients with dyslipidemia and elevated LDL-C, fibrates and niacins can be