Evolution of Omega-3 Fatty Acid Therapy and Current and Future Role in the Management of Dyslipidemia

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KEYWORDS

• Omega-3 fatty acids • Omega-3 icosapent ethyl • Omega-3 carboxylic acids • Hypertriglyceridemia • Residual risk • Dyslipidemia

KEY POINTS

- Newer omega-3 fatty acid formulations have improved bioavailability and triglyceride-lowering efficacy.
- Omega-3 fatty acids have been shown to reduce cardiovascular risk in certain high-risk subgroups.
- Omega-3 fatty acids provide cardiovascular protection through multiple mechanisms, including lipid-lowering and non–lipid-altering pathways.
- Although there is no evidence of significant harm, data to suggest significant benefit in event reduction rates with omega-3 fatty acids are lacking.
- Ongoing large, randomized, controlled trials in high-risk patients are highly anticipated.

INTRODUCTION

The benefits of omega-3 fatty acids have been recognized since the beginning of the 20th century; however, the first US Federal Drug Administration (FDA)–approved formulation was not available until 2004. Since that time, newer formulations consisting of omega-3 carboxylic acids or pure eicosapentaenoic acid (EPA) ethyl esters have been developed. Omega-3 fatty acids are most recognized for their ability to reduce serum triglycerides; however, there has been debate regarding their role in the medical armamentarium for the treatment of hypertriglyceridemia or other forms of dyslipidemia. The most recent recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on cholesterol management[1] published in 2013 do not suggest a major role of omega-3 fatty acid therapy in the treatment of dyslipidemia. This diminished role is predominantly because large trials studying nonstatin cholesterol-lowering medications showed lack of significant benefit. Subgroup analyses of those trials looking at subjects with elevated triglycerides and low high-density

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lipoprotein cholesterol (HDL-C), an unfavorable pattern of dyslipidemia, suggest there may in fact be a benefit. Current trials are ongoing with newer omega-3 fatty acid formulations to determine if patients at increased risk for atherosclerotic cardiovascular disease derive benefit from therapy. This article discusses the evolution of omega-3 fatty acid therapy as well as its current and future role in the treatment of dyslipidemia.

AVAILABLE OMEGA-3 FATTY ACID FORMULATIONS

The first omega-3 fatty acid formulation, omega-3 acid ethyl esters, was approved by the FDA in 2004 under the trade name Omacor (Reliant Pharmaceuticals, Liberty Corner, NJ) for the treatment of triglyceride levels of 500 mg/dL or more. It was renamed to Lovaza in 2007 (GlaxoSmithKline, Brentford, UK); however, Omacor is still available outside of the United States. Icosapent ethyl (Vascepa, Amarin Pharmaceuticals, Bedminster, NJ) was approved in 2012 for the treatment of severe hypertriglyceridemia (triglycerides of $\geq$500 mg/dL). Icosapent ethyl differed from the initial omega-3 fatty acid formulation by containing pure EPA ethyl esters rather than both EPA and docosahexaenoic acid (DHA). In 2014, omega-3 carboxylic acids (Epanova, AstraZeneca, Wilmington, DE) gained approval for the treatment of severe hypertriglyceridemia (triglycerides of $\geq$500 mg/dL). Omega-3 carboxylic acids consist of free fatty acids rather than a prodrug form; they have improved bioavailability and can be taken independently of meals because they are not reliant on hydrolysis by pancreatic lipase for absorption.

Momentum for the development of supplemental omega-3 fatty acids came in part from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione trial published in 1999[2] and further encouraged by the Japan EPA Lipid Intervention Study (JELIS) published in 2007.[3] The GISSI-Prevention trial showed that, in an Italian population, the administration of 1 g/d of polyunsaturated fatty acids to patients who experienced a myocardial infarction in the past 3 months reduced the primary endpoint of death, nonfatal myocardial infarction, and stroke by 10% to 15% at a follow-up of 3.5 years. The reduction in the primary endpoint was largely driven by a reduction in deaths.[2] JELIS suggested a benefit of adding omega-3 fatty acids to a statin, because there was a decrease in major adverse cardiovascular events (MACE) with a 19% risk reduction in those taking both compared with those only taking a statin over 5 years of follow-up, with more benefit seen in those on therapy for secondary prevention.[3] More recently, the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial has demonstrated the triglyceride-lowering ability of the omega-3 carboxylic acids, with a 25.5% to 30.9% reduction after 12 weeks compared with 4.3% in controls given olive oil in patients with severe hypertriglyceridemia (triglycerides of $\geq$500 mg/dL).[4]

Of the available formulations within the United States, omega-3 acids ethyl esters have been the most widely prescribed, in part because of their longer time on the market and generic options. In the last few years, studies comparing the ethyl esters and newer formulations suggest that greater benefit can be expected from the newer forms owing to their improved bioavailability. The Epanova compared to Lovaza in a pharmacokinetic single-dose evaluation (ECLIPSE) study demonstrated that omega-3 carboxylic acids, which are already in the free fatty acid form, result in about a 4-fold increase in bioavailability compared with omega-3 acid ethyl esters when taken with a low-fat meal.[5] ECLIPSE II similarly demonstrated greater EPA and DHA serum levels with omega-3 carboxylic acid use compared with omega-3 acids ethyl esters while on a low-fat diet over a longer observation period of 14 days.[6] Greater triglyceride-lowering ability was found with omega-3 carboxylic acids.

OMEGA-3 FATTY ACIDS' BENEFITS AND MECHANISM OF ACTION

Omega-3 fatty acids are best known for their triglyceride-lowering ability. Earlier formulations of EPA and DHA demonstrated about a 20% reduction,[7,8] whereas EVOLVE found closer to a 30% reduction in serum triglycerides with omega-3 carboxylic acids.[4,5] There are numerous proposed mechanisms to account for these findings, which include decreased hepatic very low-density lipoprotein (VLDL) synthesis and increased triglyceride clearance from the serum. One such mechanism is a decrease in VLDL triglyceride synthesis by altering transcription factors such as sterol regulatory element-binding proteins and peroxisome proliferator-activated receptors involved in triglyceride synthesis in the hepatocyte.[9,10] It is possible that EPA serves as a poor substrate for VLDL triglycerides, leading to lipid-poor VLDL rather than triglyceride-rich VLDL secretion into the serum.[11,12] Omega-3 fatty acids also increase serum clearance of triglyceride-rich lipoproteins by increased lipoprotein lipase activity.[10]

As demonstrated most recently in EVOLVE, omega-3 fatty acids induce favorable changes in