



Omacor (omega-3-acid ethyl esters)

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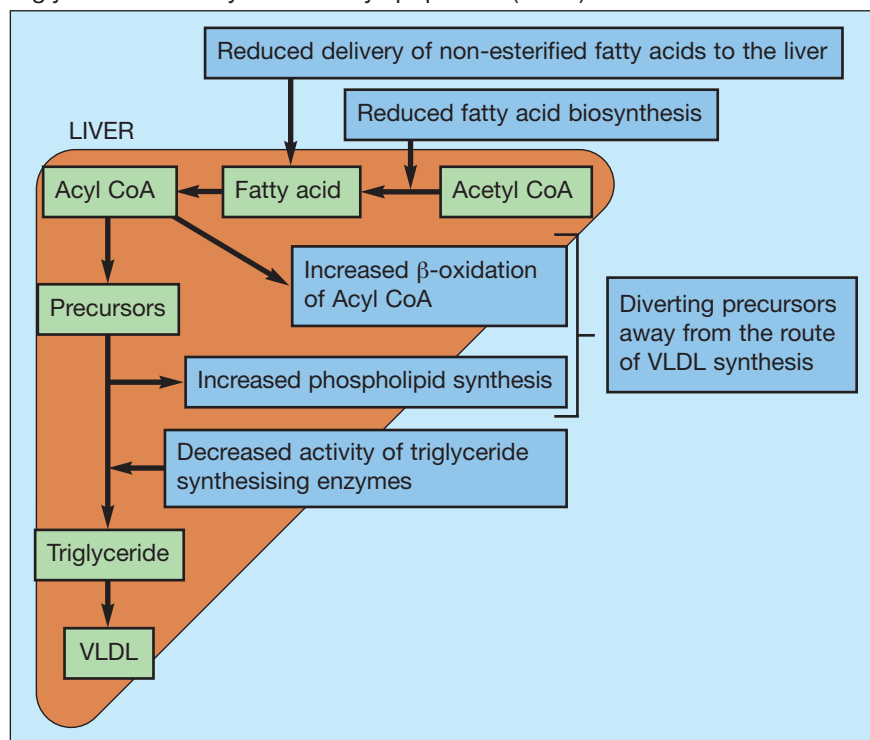
Introduction

A role for omega-3 polyunsaturated fatty acids (PUFA) in the prevention of cardiovascular disease (CVD) was first recognised in the 1970s. Many studies have since demonstrated an association between consumption of omega-3 PUFA and reduced cardiovascular mortality rate.¹ Omacor is a purified preparation of fish oil containing approximately 92% omega-3 PUFA (46% eicosapentaenoic acid [EPA], 38% docosahexaenoic acid [DHA], and 8% other omega-3 PUFA). It is licensed in the UK for use as an adjunct to diet and statin therapy in the treatment of hypertriglyceridaemia and as an adjunct therapy in secondary prevention for adults with myocardial infarction (MI) in the preceding three months.

Pharmacology

Omega-3 PUFA decrease hepatic secretion of triglycerides and triglyceride-rich very low density lipoprotein (VLDL).² The molecular mechanisms by which this occurs remain uncertain. In rats, the most consistently observed effect after omega-3 PUFA consumption was reduced hepatic fatty acid (FA) synthesis.² Other possible mechanisms include reduced delivery of non-esterified FAs to the liver leading to reduced FA substrate availability, upregulation of FA β -oxidation in the liver, decreased activity of triglyceride-synthesising enzymes, and increased phospholipid synthesis diverting diacylglycerol away from VLDL production (Figure 1). Omega-3 PUFA may also upregulate lipoprotein lipase, increasing removal of triglycerides from VLDL and chylomicron particles.¹ Various mechanisms of action have been proposed to explain the beneficial effect of Omacor in secondary prevention of CVD. *In vitro* studies

Figure 1. Possible pharmacological actions of omega-3 polyunsaturated fatty acids (PUFA) in liver and peripheral tissues leading to reduced triglyceride and very low density lipoprotein (VLDL) levels in blood



suggested anti-arrhythmic effects, which may be directly mediated by incorporation of DHA and EPA into membrane phospholipids, stabilisation of myocyte ion channels, and enhanced autonomic regulation.¹ Increased omega-3 PUFA content of cell membranes is believed to increase heart rate variability, which may contribute to a protective effect against sudden cardiac death.¹ Cardiovascular effects demonstrated in meta-analyses include modest but statistically significant reductions in heart rate and blood pressure.¹ Improvements in endothelial function and anti-inflammatory, antithrombotic as well as anti-atherogenic effects have also been proposed as possible mechanisms.

Trials of safety and efficacy

Five randomised double-blind multicentre clinical studies of eight to 24 weeks' duration have assessed the therapeutic efficacy of Omacor in the treatment of hypertriglyceridaemia, as monotherapy or in combination with a statin. Omacor (4g/day) monotherapy reduced triglyceride (-45%; $p < 0.0001$), total cholesterol (-15%; $p < 0.001$) and VLDL cholesterol (VLDL-C, -32%; $p < 0.001$) levels, and increased high density lipoprotein cholesterol (HDL-C, +13%; $p < 0.05$) levels compared with placebo after 16 weeks.¹ Combination therapy of Omacor (4g/d) and simvastatin (10–40mg/d), compared with placebo + simvastatin (10–40mg/d), improved

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triglyceride (-18.6% to -28.2% *vs* -3.5% to +12.8%; $p < 0.005$) and VLDL-C (-23.8% to -34.2% *vs* -2.8% to -10.0%; $p < 0.005$) levels after eight to 24 weeks in three different studies. In another study, combination therapy with Omacor (4g/d) and atorvastatin (10mg/d), compared to placebo + atorvastatin (10mg/d), improved triglyceride (-45.4% *vs* -26.9%; $p < 0.0001$) and VLDL-C (-54.3% *vs* -37.0%; $p < 0.0001$) levels after eight weeks' treatment.¹ In summary, Omacor (4g/d), as monotherapy or in combination with simvastatin/atorvastatin, reduced triglyceride and VLDL-C levels more than placebo; however, its effects on HDL-C and LDL-C levels have not been consistently reported in clinical studies.

Evidence supporting a role for Omacor in primary prevention of CVD is scanty. There is a lack of randomised controlled trials (RCTs) using pharmacological preparations of omega-3 PUFA; most data are derived from case-control and prospective cohort studies of dietary modification, which do not all suggest benefit.

The largest body of evidence for Omacor in secondary prevention of CVD comes from the GISSI-Prevenzione study (11 324 participants; mean follow-up 3.5 years).³ In patients with recent MI (<three months), Omacor (1g/d) decreased the incidence of the primary clinical endpoint (all-cause mortality, non-fatal MI and non-fatal stroke) compared with controls (relative risk reduction 15%; $p = 0.023$).³ These benefits were attributable to reduced mortality, specifically cardiovascular deaths and sudden deaths, with no difference in risk of non-fatal stroke or MI. Pharmacoeconomic analysis based on these findings confirmed cost-effectiveness of Omacor in addition to other prophylactic treatments as a secondary prevention strategy initiated in the first three months post-MI. In contrast, preliminary data from the OMEGA study of Omacor in patients three to 14 days post-MI indicated no significant difference in sudden cardiac death (primary endpoint) or various secondary endpoints between the Omacor and placebo groups.¹

Omacor is generally well tolerated; the most common side effect is mild gastrointestinal disturbance. It is

advisable to closely monitor patients concomitantly receiving anticoagulants and omega-3 PUFA because of a theoretical risk of increased bleeding. Omacor may also increase the risk of pancreatitis in patients with severe hypertriglyceridaemia (>20mmol/L); this requires further quantitative evaluation as reduction in risk of pancreatitis is a key aim of treatment of hypertriglyceridaemia.

Specific evidence for use in diabetes

The typical pattern of dyslipidaemia in type 2 diabetes (T2DM) is characterised by hypertriglyceridaemia, raised total cholesterol and LDL-C, and low levels of HDL-C. Despite the triglyceride-lowering effects of omega-3 PUFA, there is little evidence for specific benefits of pharmacological preparations such as Omacor in patients with diabetes. Current NICE guidelines for T2DM recommend fibrate therapy for targeted reduction of triglycerides in patients with either raised triglycerides (>4.5mmol/L) despite optimal glycaemic control or moderately raised triglycerides (2.3–4.5mmol/L) with high cardiovascular risk. Omega-3 PUFA preparations are considered second-line if lifestyle measures and fibrate therapy are ineffective.

A recent Cochrane systematic review of the use of omega-3 PUFA in T2DM (23 RCTs; nil used Omacor as the preparation of omega-3 PUFA) demonstrated that omega-3 PUFA (mean 3.5g/d) decreased triglyceride and VLDL-C levels by 0.45mmol/L ($p < 0.00001$) and by 0.07mmol/L ($p < 0.05$) respectively.⁴ Despite isolated reports of impaired glycaemic control associated with use of omega-3 PUFA in patients with diabetes, the Cochrane review demonstrated that omega-3 PUFA did not significantly alter HbA_{1c}, fasting glucose, fasting insulin or body weight.⁴ Extrapolation of the clinical impact of modest lowering of triglycerides in patients with T2DM with omega-3 PUFA supplementation is difficult due to the lack of trials using vascular events or mortality as clinical endpoints.

Ongoing studies investigating a role for Omacor in patients with diabetes include the ASCEND, AFFORD and ORIGIN trials.

Key points

- Omega-3 polyunsaturated fatty acids decrease hepatic secretion of triglycerides and VLDLs
- Omacor (4g/day), either as monotherapy or in combination with simvastatin/atorvastatin, reduces triglyceride and VLDL cholesterol levels in blood more than placebo
- Omega-3 PUFA preparations should be considered second-line treatment if lifestyle measures and fibrate therapy are ineffective in improving hypertriglyceridaemia in patients with diabetes
- There may be a role for Omacor in secondary prevention of cardiovascular disease in patients with recent myocardial infarction

Discussion

Whether patients with diabetes should receive pharmacological treatment routinely used in post-MI secondary prevention is not entirely clear. Currently, Omacor cannot be recommended for routine use in patients with diabetes due to the lack of evidence in terms of cardiovascular morbidity and mortality in this patient group. Omacor should be considered in patients with diabetes for the same indications as those for non-diabetic patients: as a second-line therapy for hypertriglyceridaemia and post-MI as a secondary prevention strategy. The impact of hypertriglyceridaemia and of reducing triglyceride levels on cardiovascular risk needs to be further elucidated in order to guide treatment targets for diabetic dyslipidaemia. The reduction of sudden deaths by Omacor in the GISSI-Prevenzione trial is of particular interest in the diabetes subgroup as diabetic autonomic dysfunction appears to predispose to sudden death; further studies are required to assess any clinical scope for this possible benefit of Omacor.

Conflict of interest statement

CKMH has delivered seminars sponsored by Merck. SWW has received honoraria related to advisory activities from Merck.

References

References are available at www.practicaldiabetesinternational.com.

**Omacor (omega-3-acid ethyl esters)****References**

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