

Medical affairs

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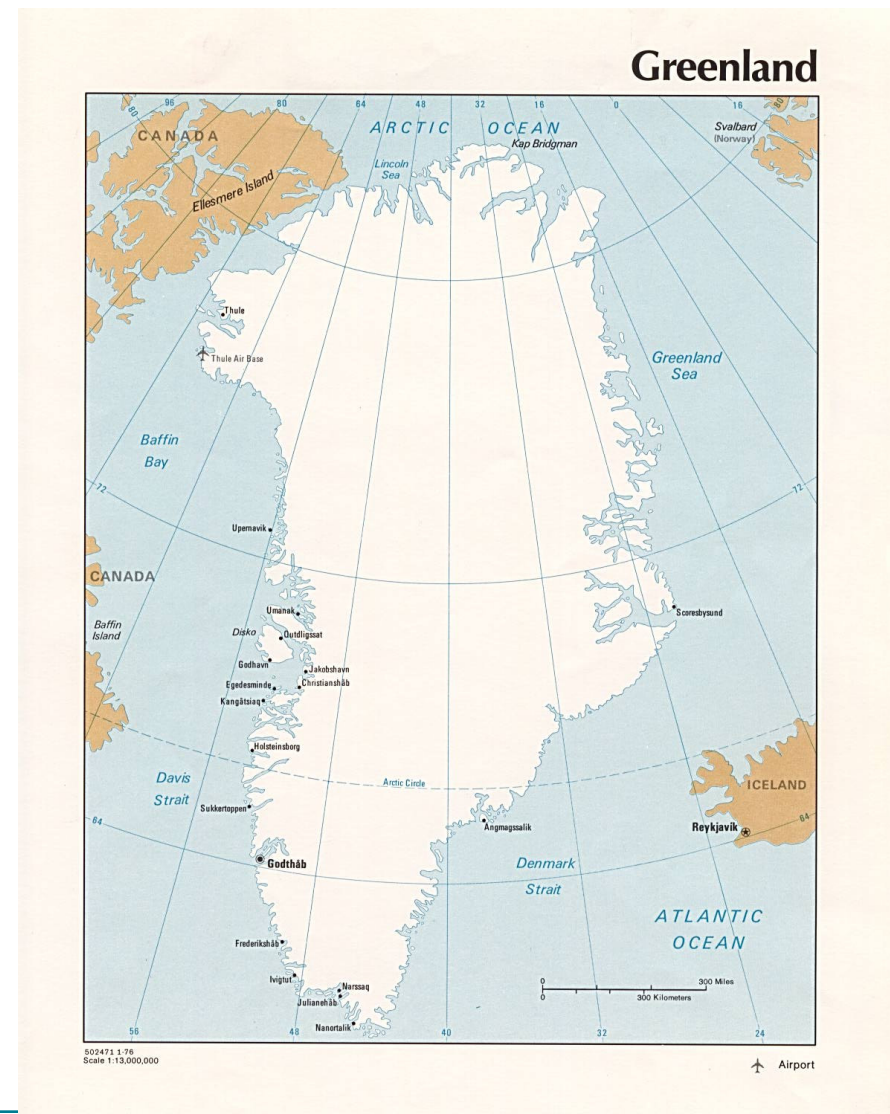


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Omega 3 – where did it all start?

- **Danish scientists explored the nature of nutrients in eskimo diet in the 70s. Paradox: high intake of fat, low incidence of cardiovascular disease**
- **The fat originated from fatty fish, seal and whale that contain high amounts of omega 3 fatty acids**
- **Bang and Dyrberg hypothesised that Omega 3 protects against cardiovascular disease**
- **Eskimos that migrate to Denmark start to develop the same diseases as danes**



Omega 3 – where did it all start?

Myocardial infarction and dietary fat intake of Eskimos versus Danes

	Eskimos	Danes
Myocardial Infarction	3	40
Energy from fat (%)	39	42
n-6 PUFA (g/d)	5	10
n-3 PUFA (g/d)	14	3
n-3/n-6	2.8	0.3
Cholesterol (mg/d)	790	420

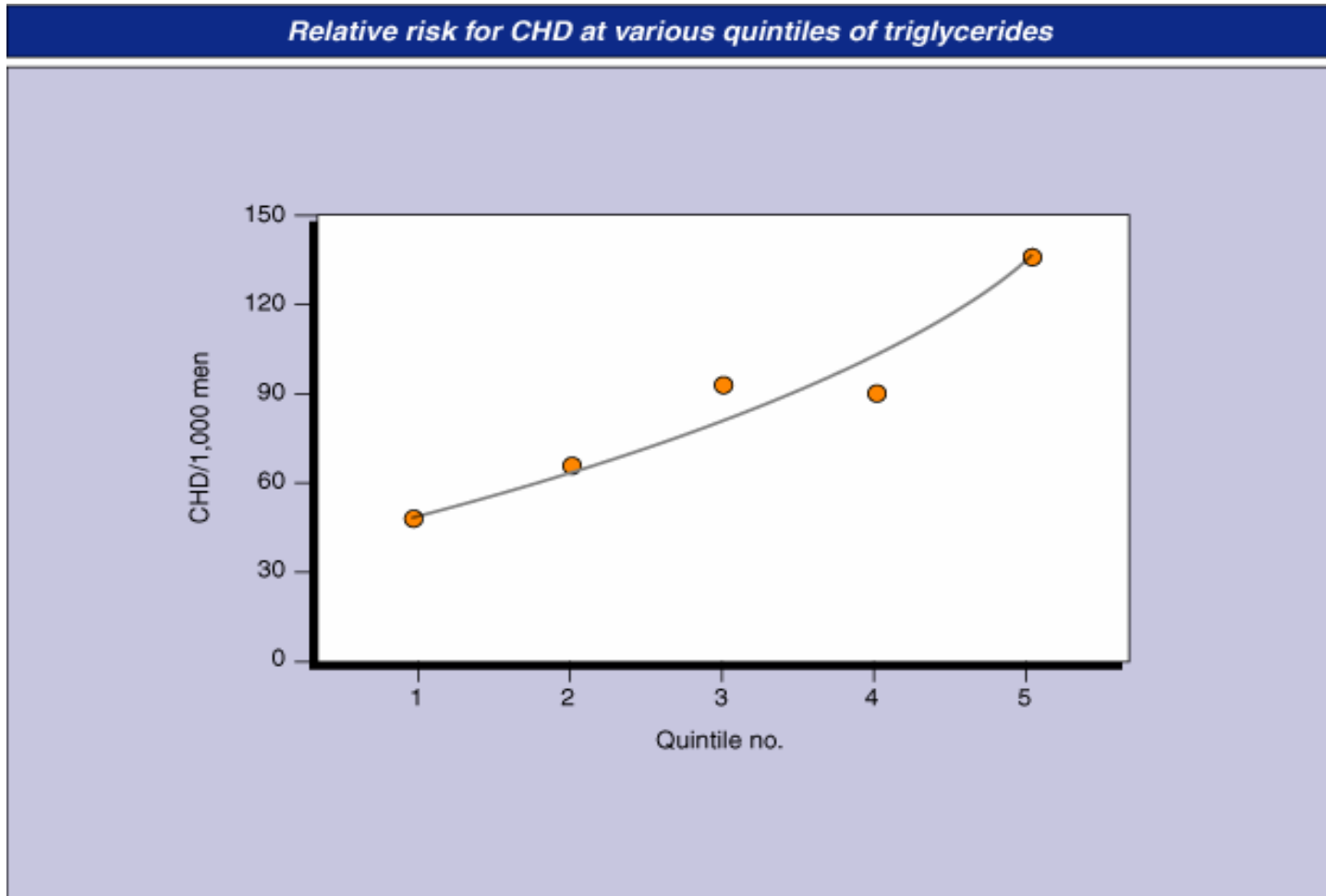
Kristensen SD et al. J Intern Med Supp 1989

Lack of atherosclerosis in aorta



Atherosclerosis is associated with cardiovascular disease

High triglyceride indication – background



Clinical trial overview

Indication	Number of clinical trials ¹	Total number of patients	Key trial names
HTG	§ 40	§ c.2,700 § Of which c.1,500 have completed trials	OM6, OM5, OM9L Durrington et al Chan et al
Post MI	§ 2	§ c.15,000 § Of which c.11,324 have completed trials	GISSI P
Atrial Fibrillation	§ 7	§ c.1,600	OM8 AFIB
Heart Failure	§ 1	§ c.7,000	GISSI HF
Primary Prevention of Cardiovascular Disease (Diabetes Type II)	§ 2	§ c.23,000	ORIGIN, ASCEND
Fixed Dose Combinations ²	§ 10	§ c.900 § Of which c.500 have completed trials	OM6, OM5

15 May, 2008

Notes
1 Finished, ongoing and under recruitment

2 Fixed Dose Combination trials are for concomitant therapy

Guidelines for treatment of high triglycerides

- **Indications and usage - Very High Triglycerides**
 - *Omacor is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (= 500 mg/dL) triglyceride levels*
- **Triglycerides > 500 mg/dl:**
 - *Indication for treatment of triglycerides prior to other lipid parameters (LDL) due to risk of pancreatitis*
- **Triglycerides > 200 mg/dl:**
 - *Non-HDL cholesterol secondary target of therapy. Aim LDL-cholesterol goal + 30 mg/dl*
- **Non-HDL cholesterol = VLDL + LDL cholesterol**
- **VLDL denotes atherogenic remnant lipoproteins**

Key issues facing existing drugs – monotherapy

Fibrates and niacin are currently the most widely used triglyceride-lowering drugs. However, their side-effects, notably elevated liver enzymes, rhabdomyolysis, glucose intolerance and flushing, are continued concerns

Drug class	1st / 2nd line	Indication	Side effects	Contraindications
HMG CoA reductase inhibitors (statins)	1st and 2nd line	Reduction of LDL levels	Myopathy Increased liver enzymes Rhabdomyolysis Proteinuria Renal Failure	<ul style="list-style-type: none"> Absolute <ul style="list-style-type: none"> – active or chronic liver disease Relative <ul style="list-style-type: none"> – concomitant use of certain drugs such as fibrates
Ezetimibe	Primarily 2nd line and in combination with statins	Reduces cholesterol uptake in the small intestine	No serious side effects	<ul style="list-style-type: none"> Patients who exhibit hypersensitivity to any component in ezetimibe
Nicotinic acid	Primarily 2nd line	HDL raising and TG lowering	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	<ul style="list-style-type: none"> Absolute <ul style="list-style-type: none"> – chronic liver disease – severe gout Relative <ul style="list-style-type: none"> – diabetes – hyperuricemia – peptic ulcer disease
Fibric acids	2nd line and in combination with statins	TG lowering and HDL raising	Dyspepsia Pancreatitis Gallstones Myopathy Unexplained non-CHD (inc cancer) deaths in WHO study	<ul style="list-style-type: none"> Absolute <ul style="list-style-type: none"> – severe renal disease – severe hepatic disease
Omacor	1 st line and in combination with statins	TG lowering and HDL raising	No serious side effects ¹	<ul style="list-style-type: none"> Patients who exhibit hypersensitivity to any component in Omacor

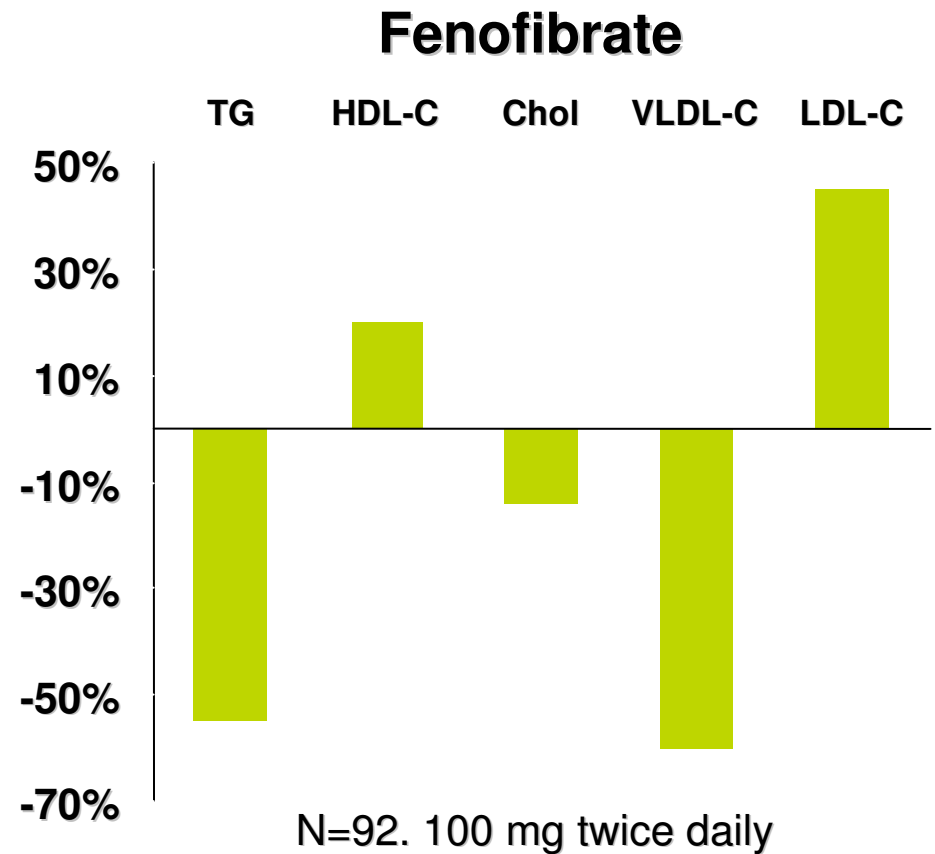
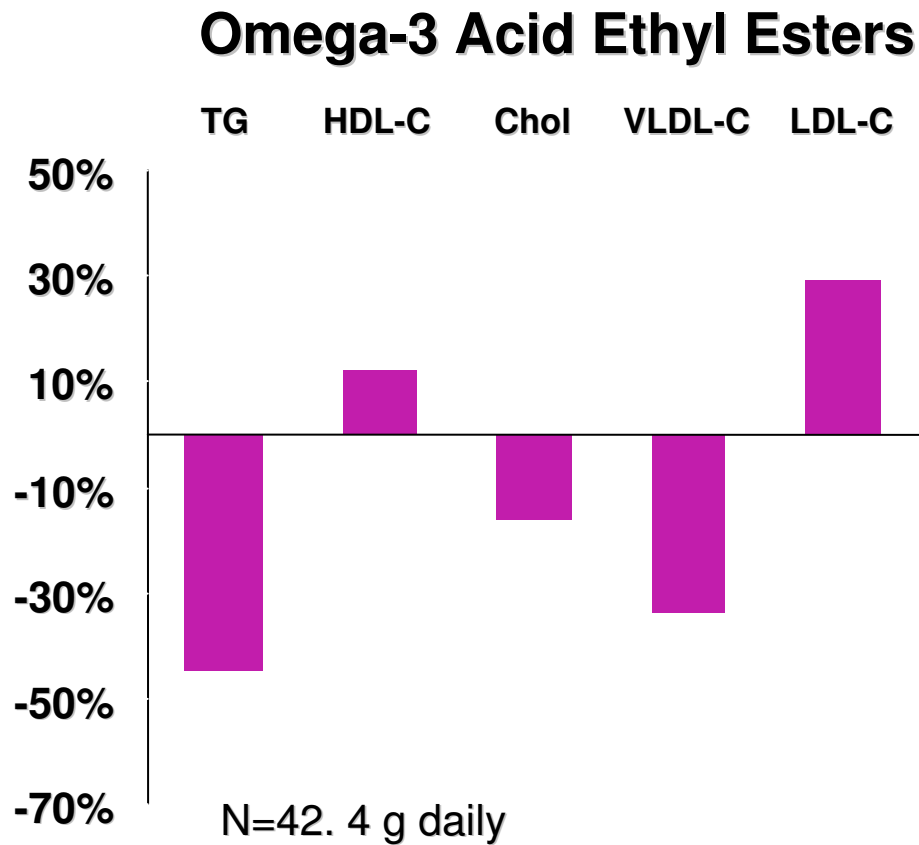
Source: Datamonitor, 2005

15 May 2008

1 See package insert

Fenofibrate and omega-3 acid ethyl esters - effects on lipid profiles

Both studies done in patients with TG >500 mg/dL
Relative Difference vs Placebo



Statin combination therapy: Overview

Rationale

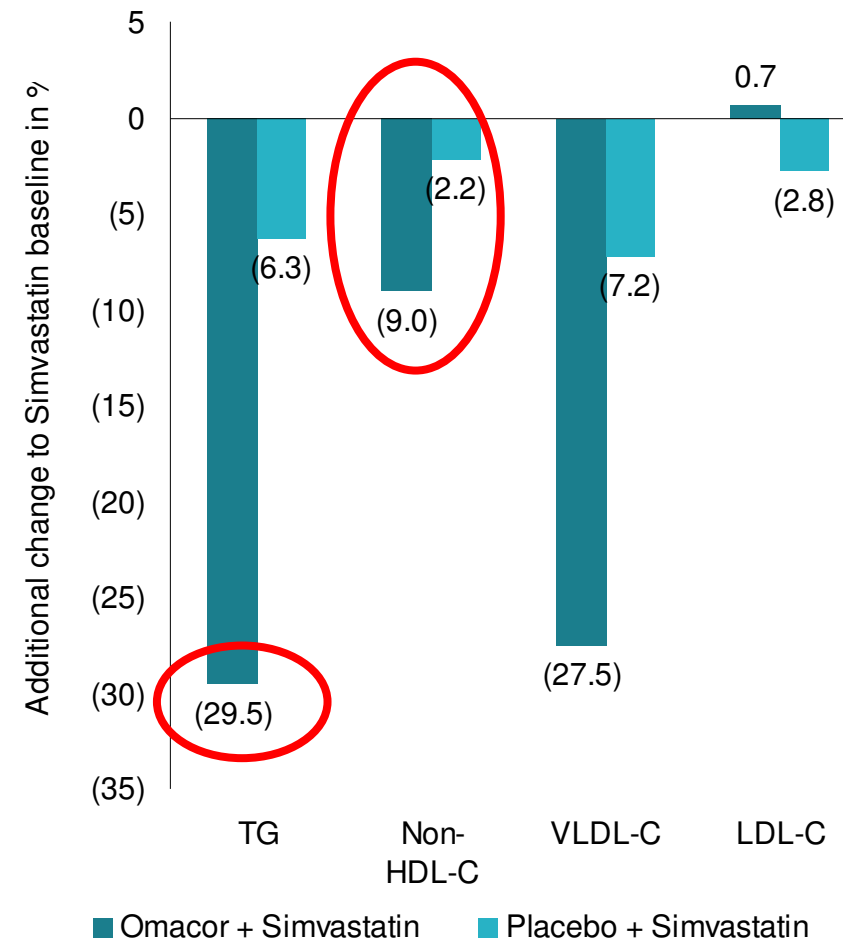
- **Omacor/Lovaza is the only approved omega-3 derived pharmaceutical which is clinically proven to reduce TG and is used in HTG and Post-MI patients, and is indicated as a concomitant therapy with statins**
- **An estimated 60 million patients take statins**
- **Monotherapy statin usage is not sufficient to meet clinical targets for triglyceride levels in all patients**
- **Fixed dose combinations with Omacor/Lovaza improves compliance and thus clinical benefits**



Strong rationale and relatively high probability of success for a fixed dose combination

Mixed dyslipidemia combination therapy – OM6 (Phase III)

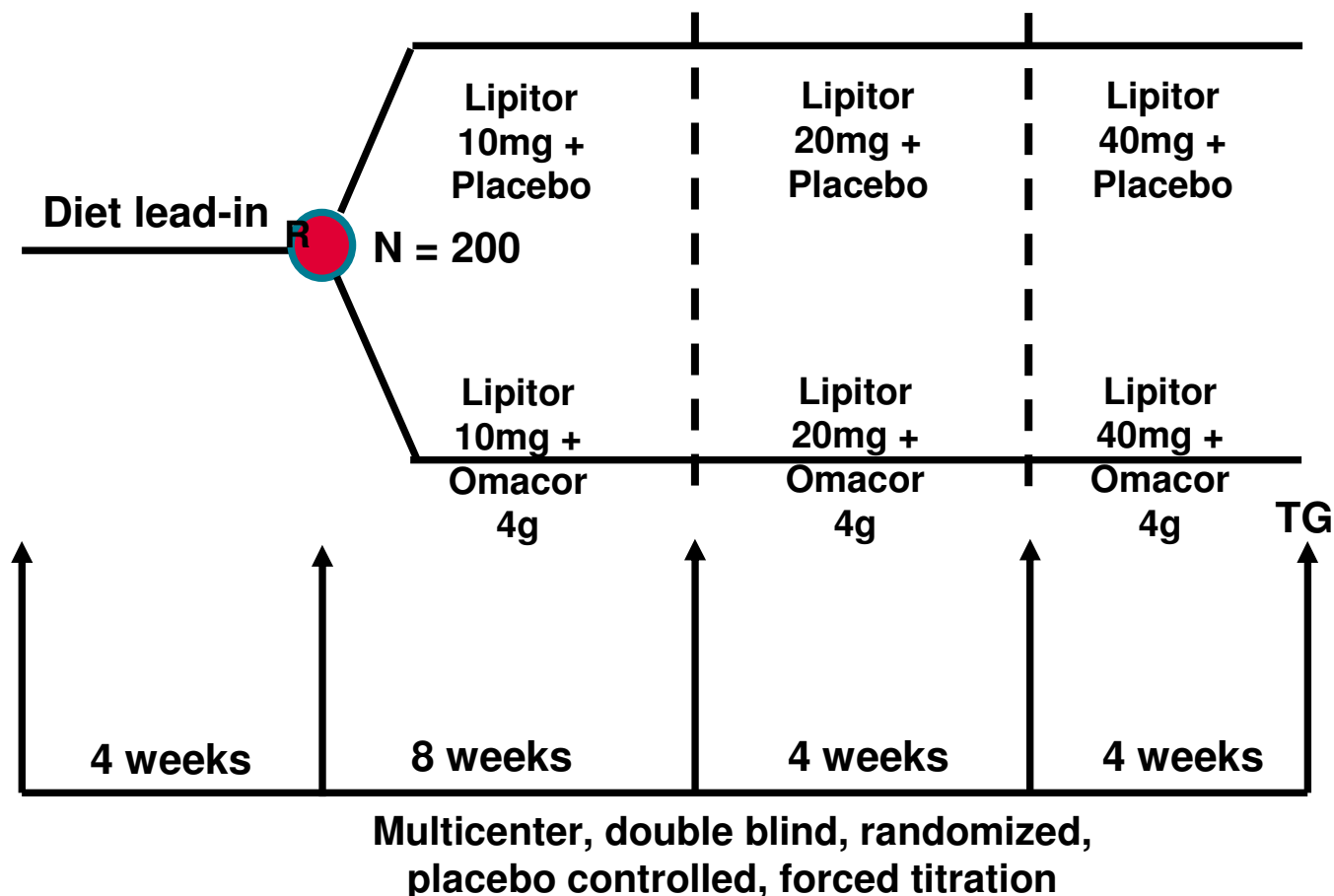
- **Objective:** Efficacy and safety of Omacor in combination with simvastatin for HTG 200-499 mg/dL patients
- **Study:** 8 week treatment (with 8 weeks run-in), 254 patients split into two groups:
 - *Omacor 4g and simvastatin 40mg*
 - *Placebo and simvastatin 40mg*
- **Primary endpoint:** Change in non-HDL-C from baseline
- **Secondary endpoint:** Change from baseline in TG and cholesterol fractions (VLDL-C, LDL-C)
- **Status:** Completed, published 2007. Included in FDA label



Clinical data included in the US label

HTG / Mixed dyslipidemia combination – OM9L

- **Objective:** Efficacy and safety of Omacor in combination with atorvastatin
- **Study:**
 - 16 weeks treatment duration (+four weeks diet lead-in),
 - triglyceride levels of 150-500mg / dl
 - LDL<20% over target NCEP while on atorvastatin treatment. Patients split into two groups
 - Omacor 4g and atorvastatin 10-40mg
 - Placebo and atorvastatin 10-40mg
- **Primary endpoint:** Change in non-HDL from baseline
- **Secondary endpoint:** Change from baseline in cholesterol fractions and other lipoproteins
- **Status:** Ongoing



McKenney demonstrated in 2006 that Omacor did not affect the pharmacokinetics of simvastatin

Pharmacokinetic study on Omacor + Simvastatin

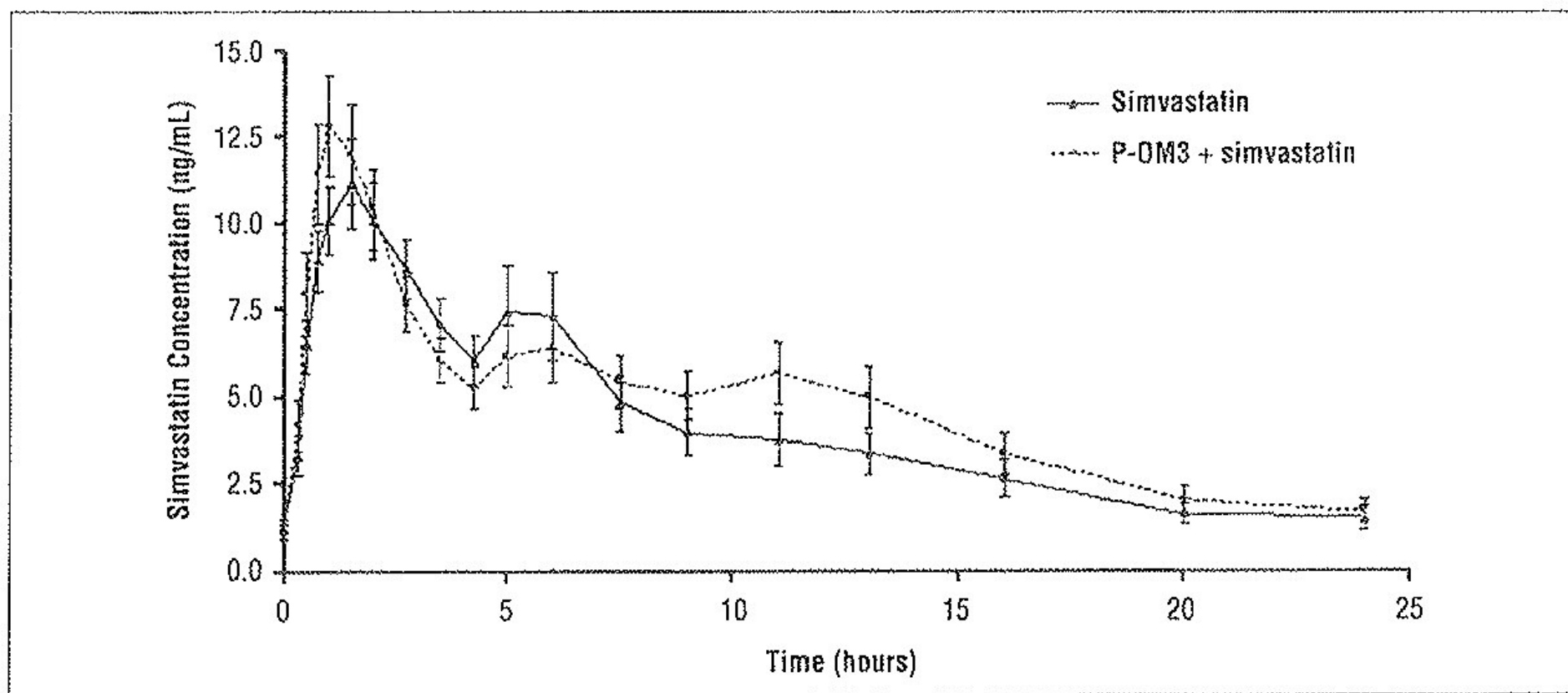



Figure 1. The mean (\pm SE) steady-state plasma concentrations of simvastatin from prescription omega-3 fatty acid ethyl esters (P-OM3) plus simvastatin versus simvastatin alone from hours 1 to 24 on day 14.

Atrial fibrillation and omega 3: Overview

Rationale

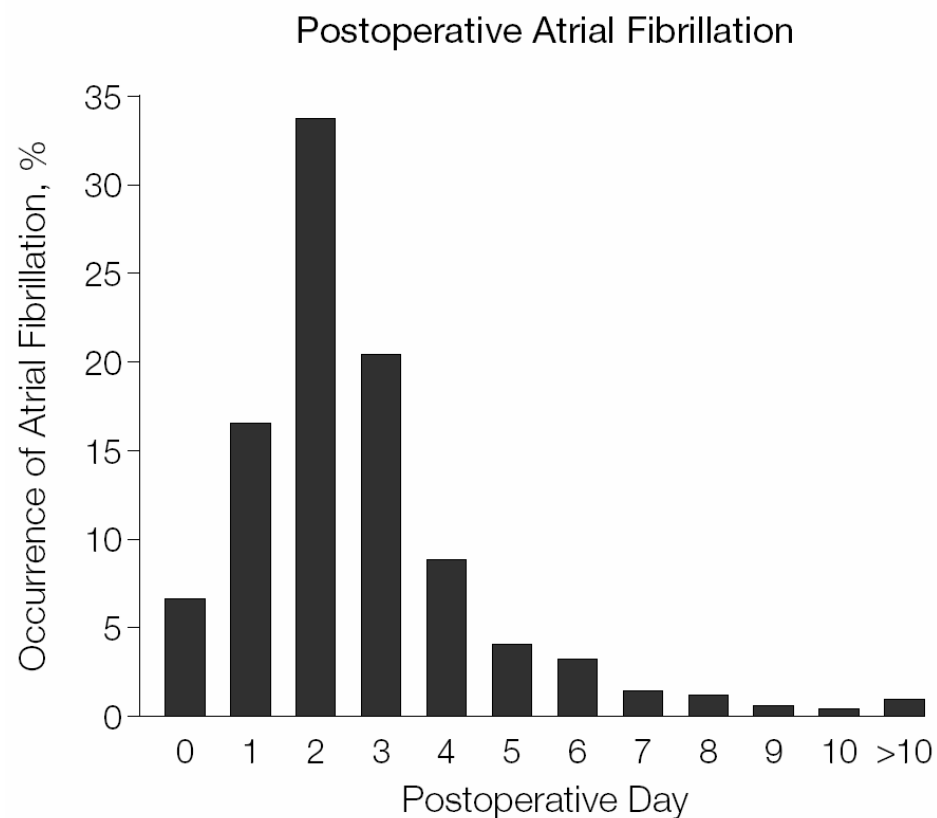
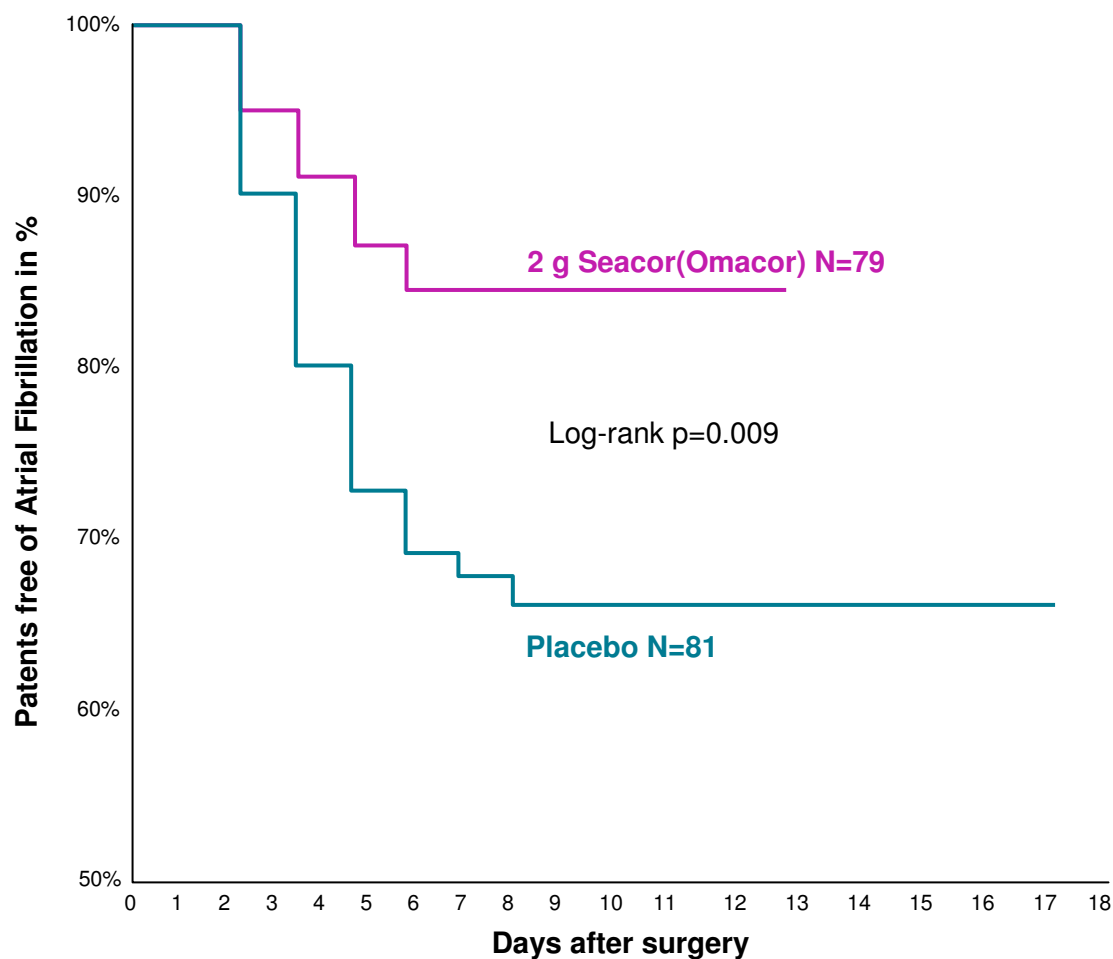
- **Epidemiological evidence of reduced incidence of AF with increased intake of EPA and DHA in 4815 elderly US adults**
- **GISSI-P showed 45% reduction in sudden death (which might be caused by cardiac arrhythmia)**
- **Animal data have shown that treatment with omega-3 fatty acids prevented arrhythmias**
- **In humans it has been shown that preoperative treatment with omega-3 fatty acids reduced the incidence of postoperative AF by more than 50% in patients following CABG surgery**



GCP study initiated to evaluate the efficacy & safety of Omacor in patients with recurrent, symptomatic AF

Atrial fibrillation: Clinical results

Omacor reduceS incidence of post operative atrial fibrillation

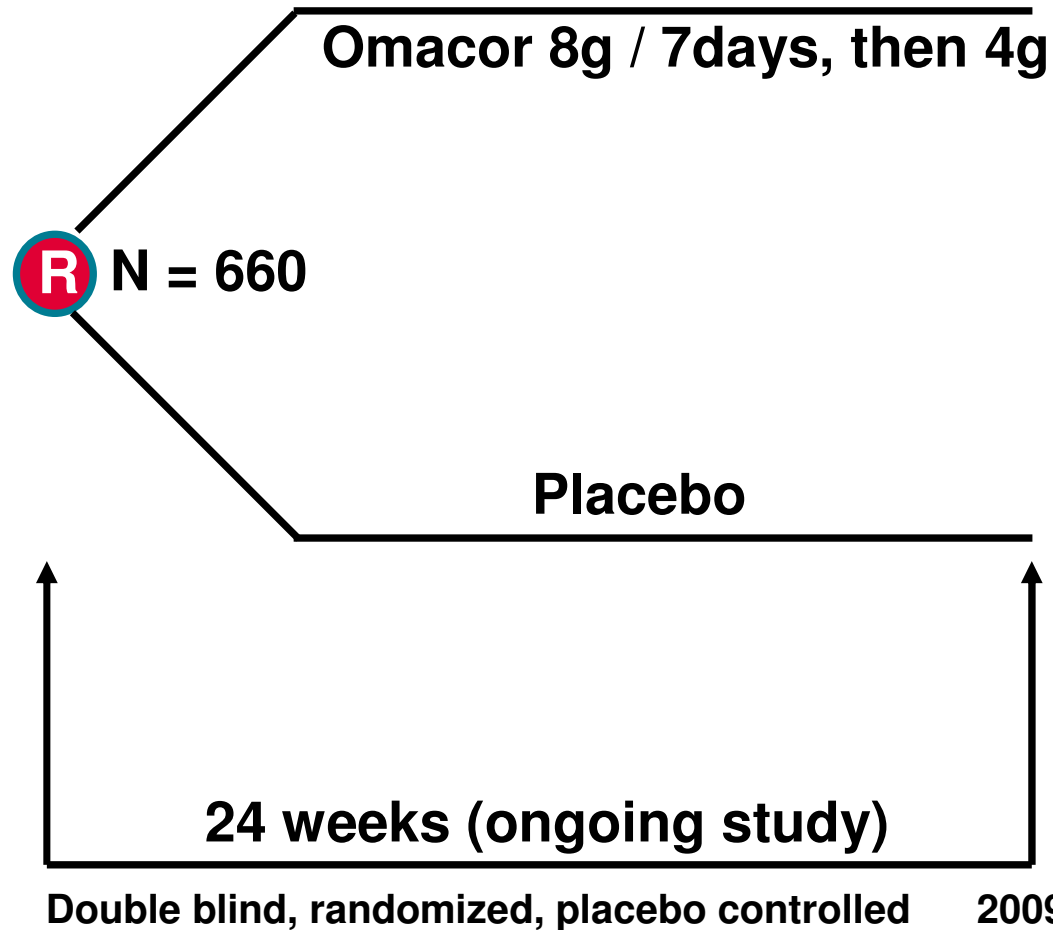


Atrial fibrillation: OM8 (ongoing)

Inclusion:

ECG evidence of paroxysmal or persistent atrial fibrillation.

Older than 18 years



Endpoint:
Prevention of atrial fibrillation relapse

Future large studies

GISSI-HF	OM8-Afib	Origin	GISSI R&P	Ascend
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2008

2009

2010

2011

2012



Several interesting studies will report the next five years