

# Medical affairs

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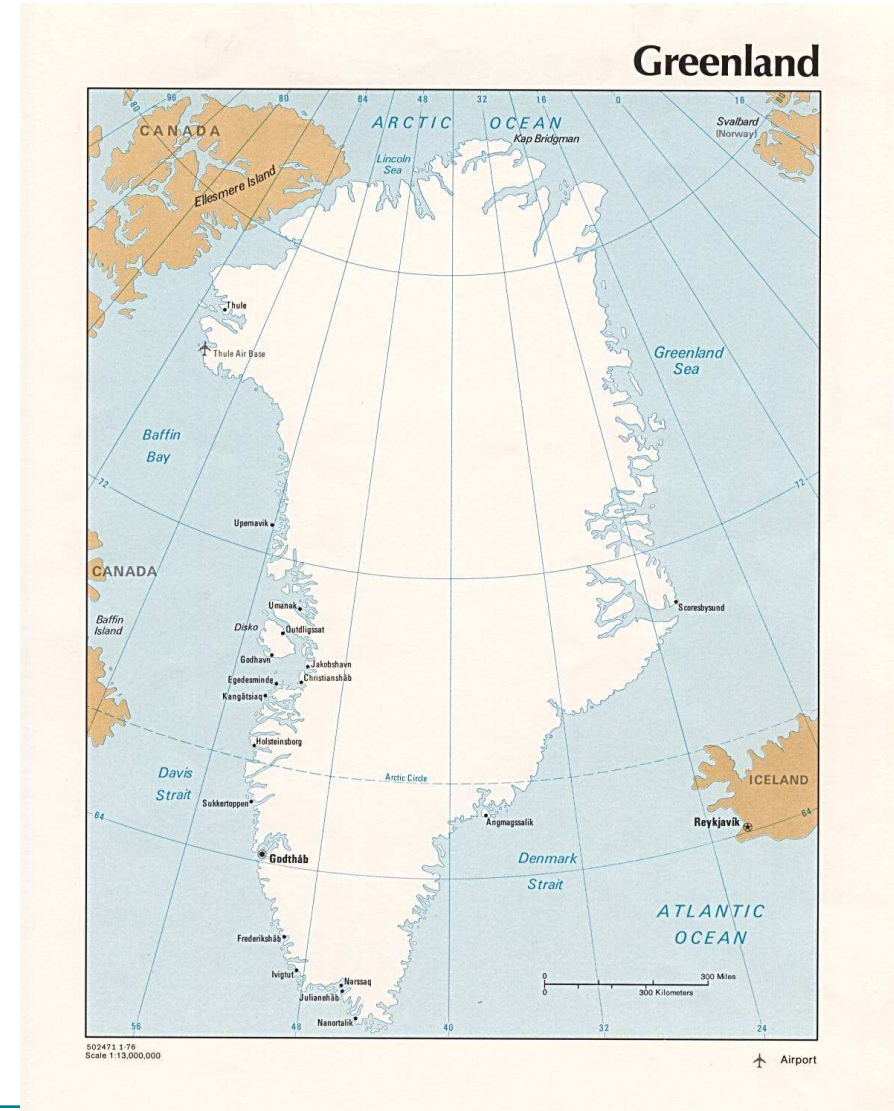
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# Omega 3 – where did it all start?

- 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



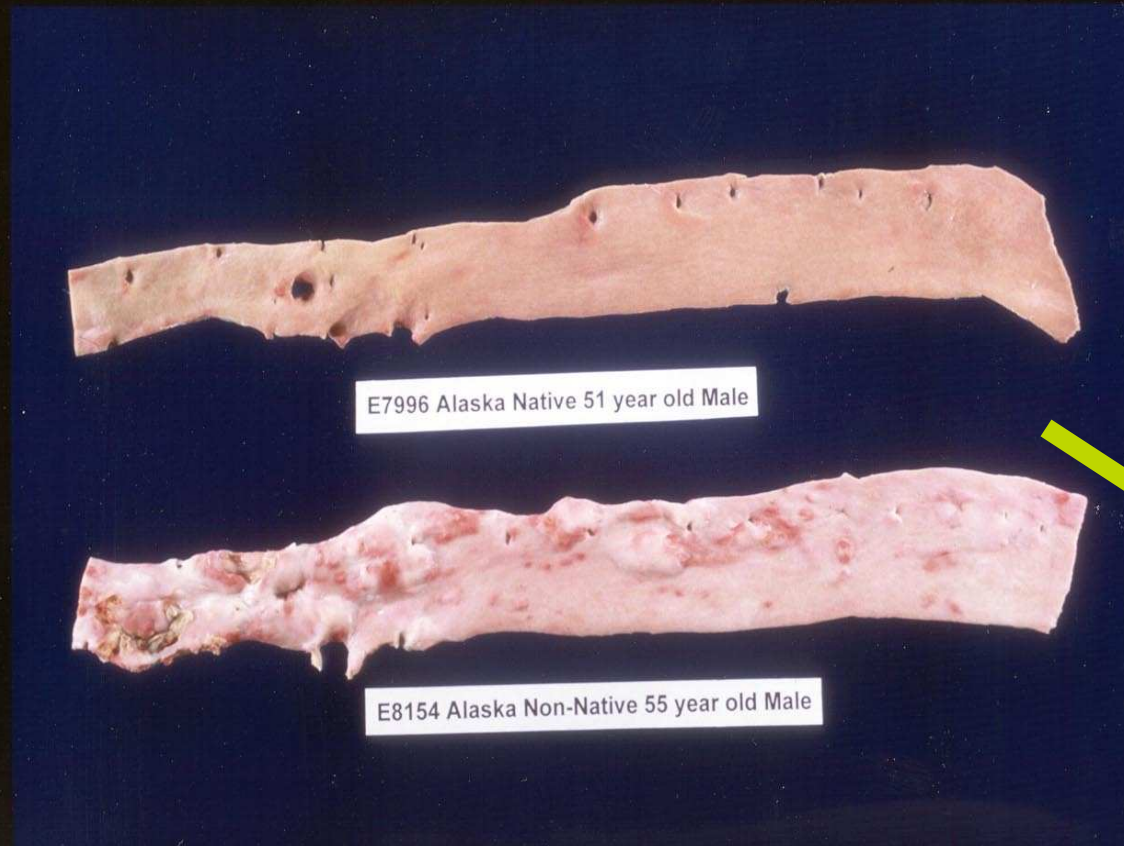
# Omega 3 – where did it all start?

## Myocardial infraction 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

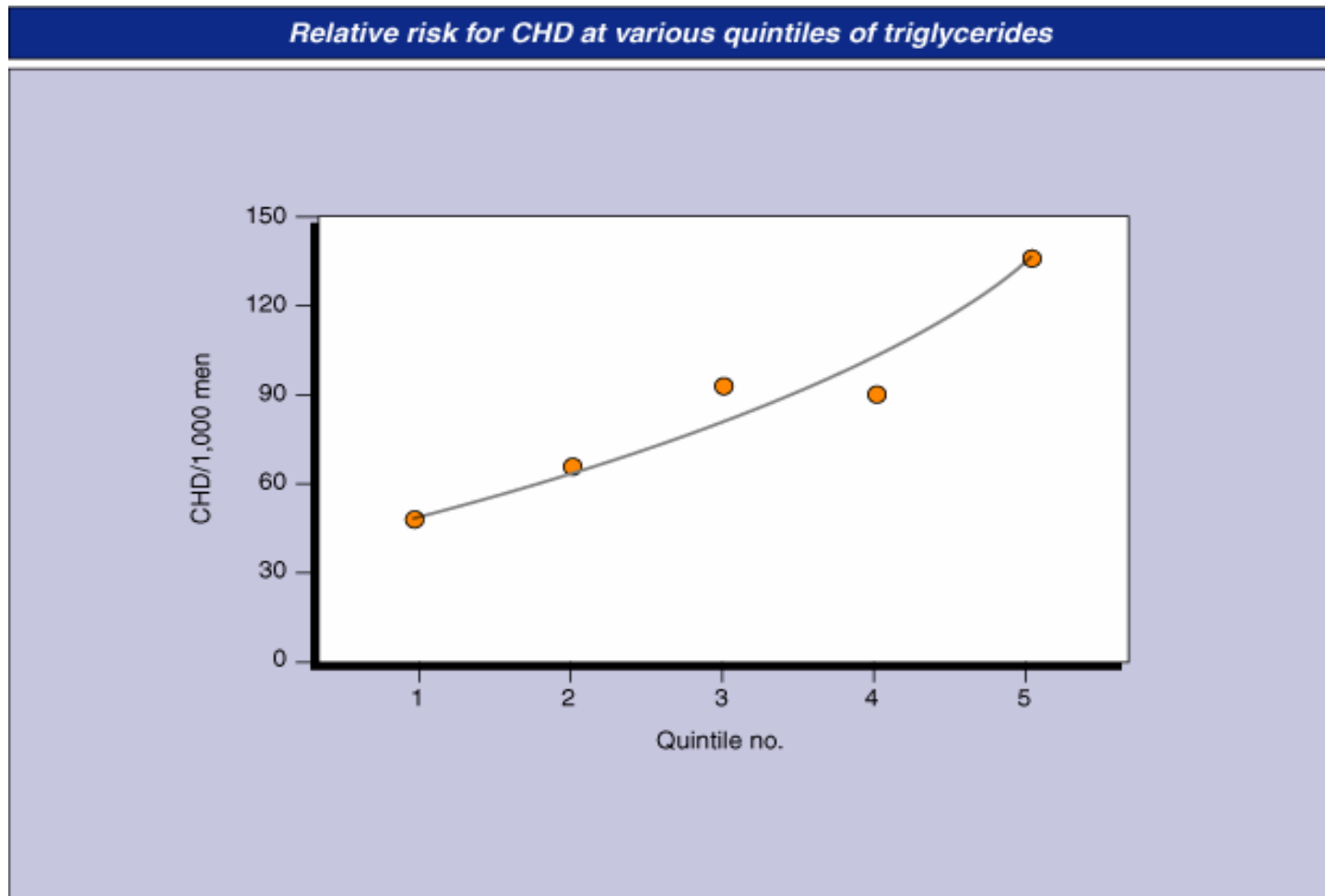
*Kristensen SD et al. J Intern Med Supp 1989*

# Lack of atherosclerosis in aorta



Atherosclerosis is associated with cardiovascular disease

# High triglyceride indication – background



# Clinical trial overview

Indication	Number of clinical trials <sup>1</sup>	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 <sup>2</sup>	§ 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

- **Lovaza Indications and usage (US) - 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*
- **Omacor indications (EU)**
  - *Post Myocardial Infarction: Adjuvant treatment in secondary prevention after myocardial infarction, in addition to other standard therapy (e.g. statins, antiplatelet medicinal products, betablockers, ACE inhibitors).*
  - *Hypertriglyceridaemia: Endogenous hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response:*
    - type IV in monotherapy,
    - type IIb/III in combination with statins, when control of triglycerides is insufficient
- 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"> <li>Absolute                             <ul style="list-style-type: none"> <li>– active or chronic liver disease</li> </ul> </li> <li>Relative                             <ul style="list-style-type: none"> <li>– concomitant use of certain drugs such as fibrates</li> </ul> </li> </ul>
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"> <li>Patients who exhibit hypersensitivity to any component in ezetimibe</li> </ul>
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"> <li>Absolute                             <ul style="list-style-type: none"> <li>– chronic liver disease</li> <li>– severe gout</li> </ul> </li> <li>Relative                             <ul style="list-style-type: none"> <li>– diabetes</li> <li>– hyperuricemia</li> <li>– peptic ulcer disease</li> </ul> </li> </ul>
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"> <li>Absolute                             <ul style="list-style-type: none"> <li>– severe renal disease</li> <li>– severe hepatic disease</li> </ul> </li> </ul>
Omacor	1 <sup>st</sup> line and in combination with statins	TG lowering and HDL raising	No serious side effects <sup>1</sup>	<ul style="list-style-type: none"> <li>Patients who exhibit hypersensitivity to any component in Omacor</li> </ul>

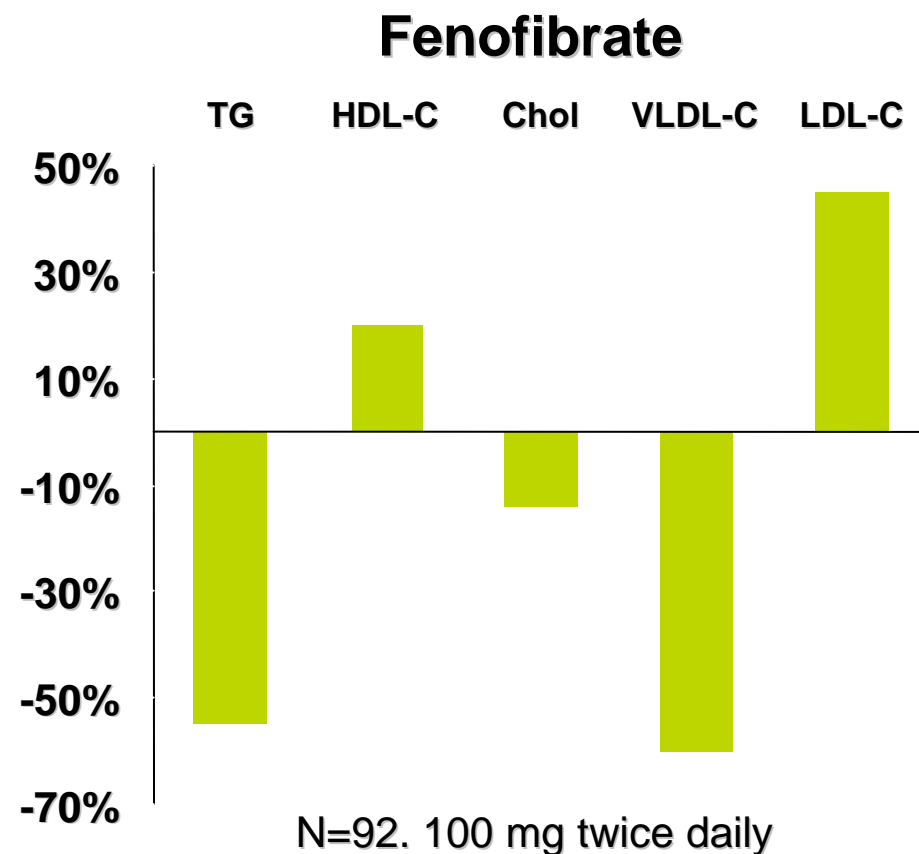
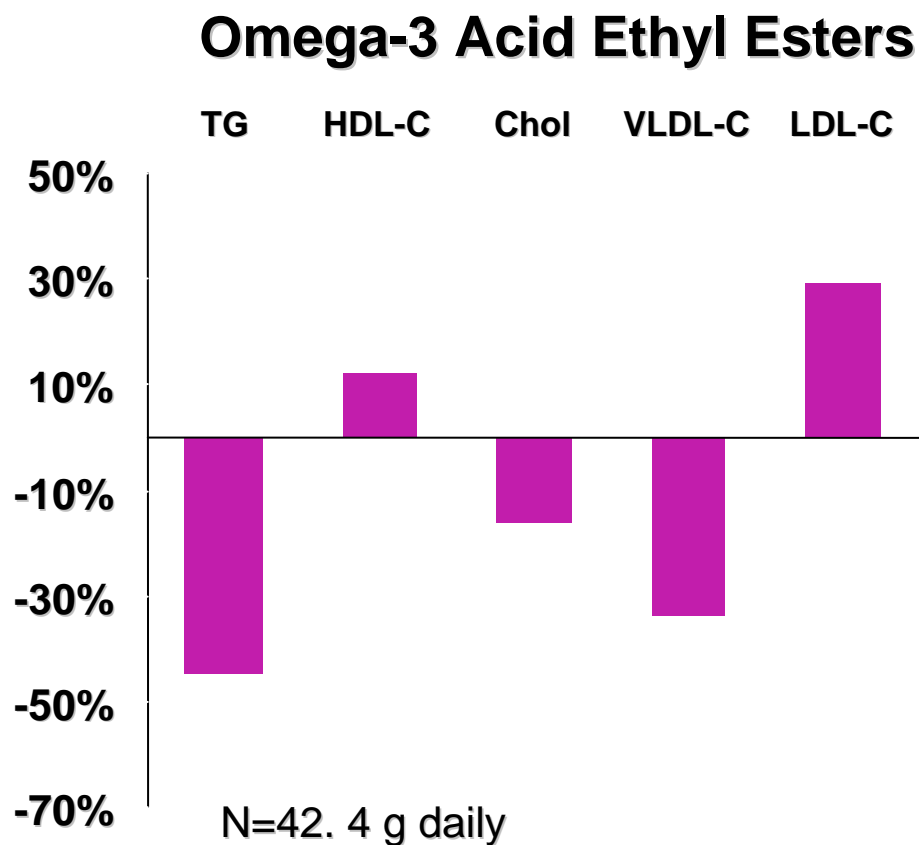
Source: Datamonitor, 2005

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

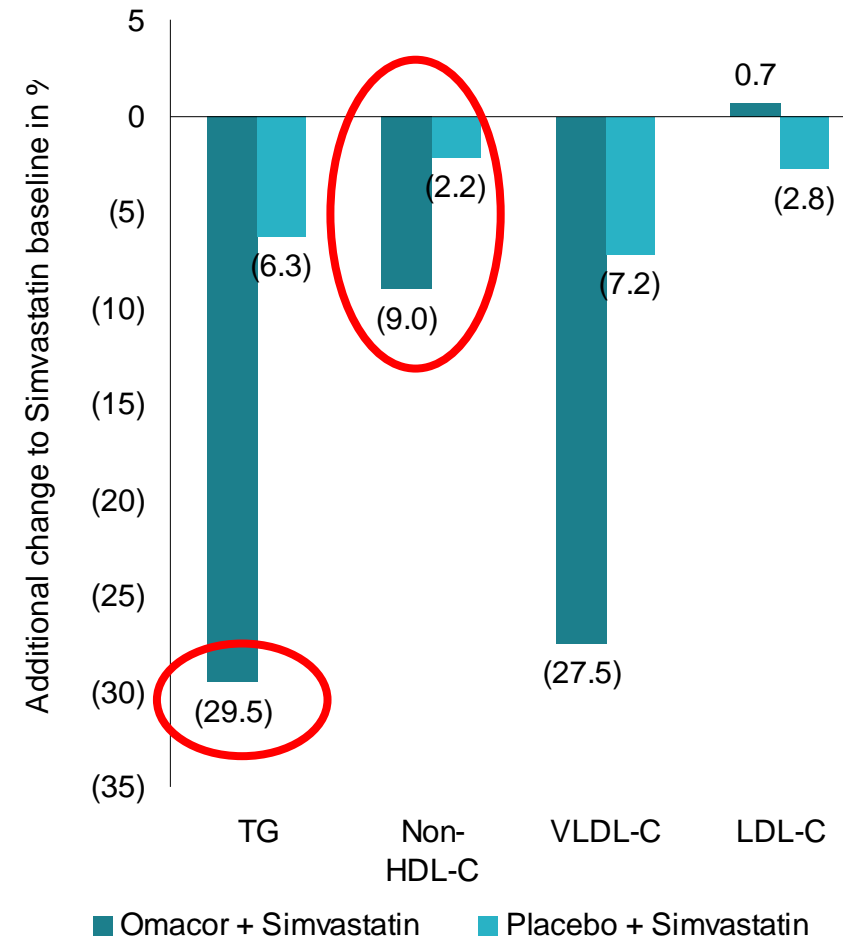
- **Omacor/Lovaza is the only approved omega-3 derived pharmaceutical which is clinically proven to reduce TG and is used in HTG and Post-MI patients, and is indicated as a concomitant therapy with statins**
- **An estimated 60 million patients take statins**
- **Monotherapy statin usage is not sufficient 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)

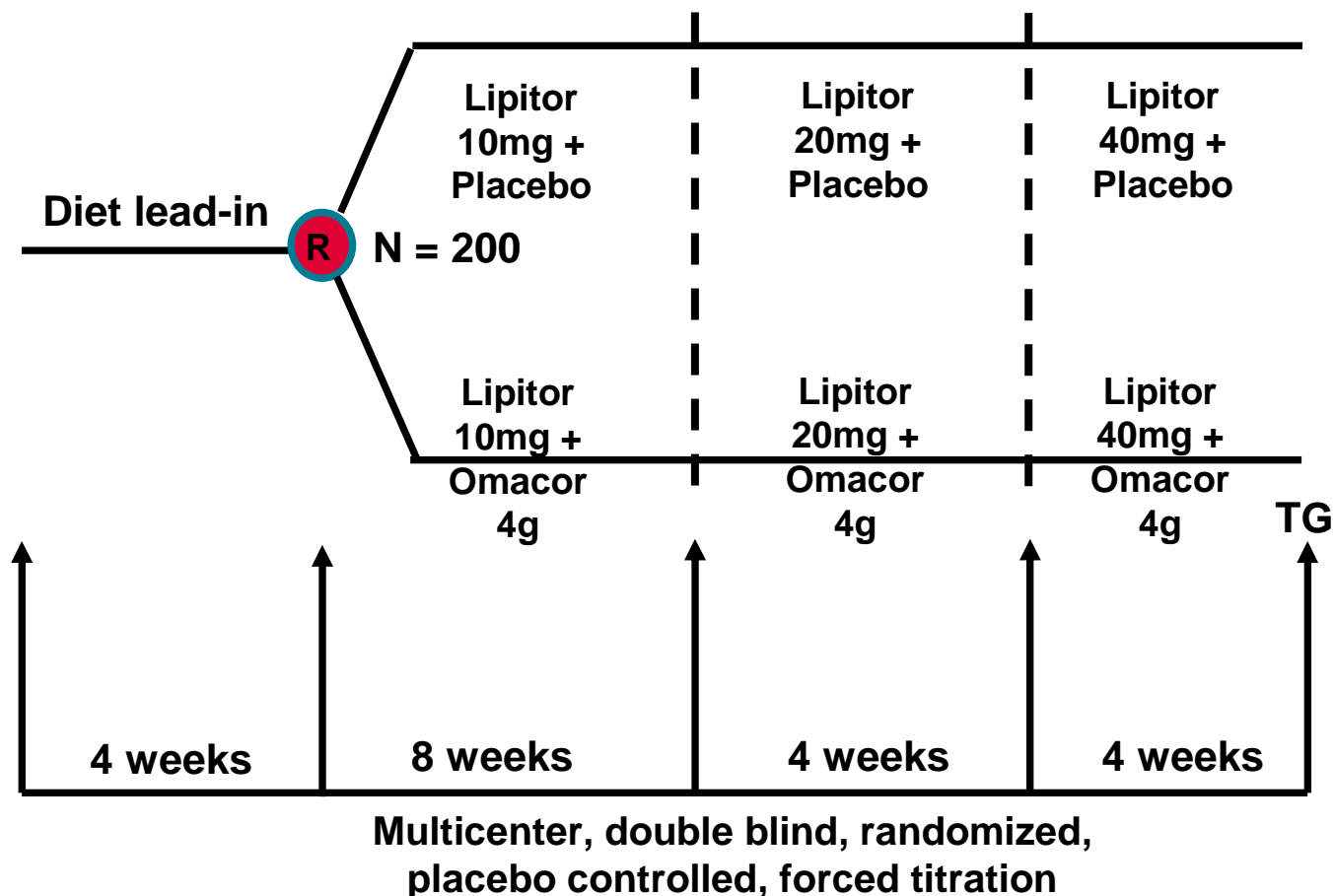
- **Objective:** Efficacy and safety of Omacor in combination with simvastatin for HTG 200-499 mg/dL patients
- **Study:** 8 week treatment (with 8 weeks run-in), 254 patients split into two groups:
  - *Omacor 4g and simvastatin 40mg*
  - *Placebo and simvastatin 40mg*
- **Primary endpoint:** Change 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

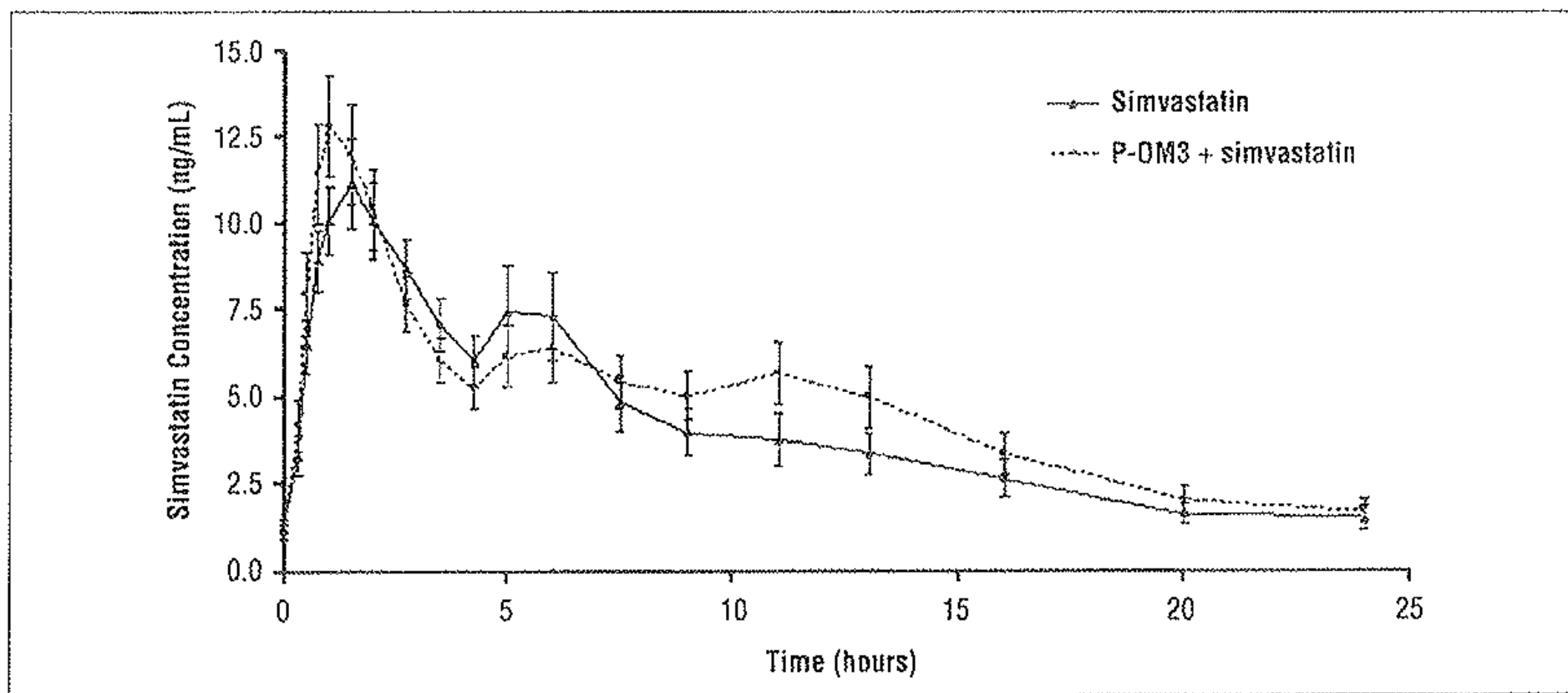


Figure 1. The mean ( $\pm$ SE) steady-state plasma concentrations of simvastatin from prescription omega-3 fatty acid ethyl esters (P-OM3) plus simvastatin versus simvastatin alone from hours 1 to 24 on day 14.

# Atrial fibrillation and omega 3: Overview

## Rationale

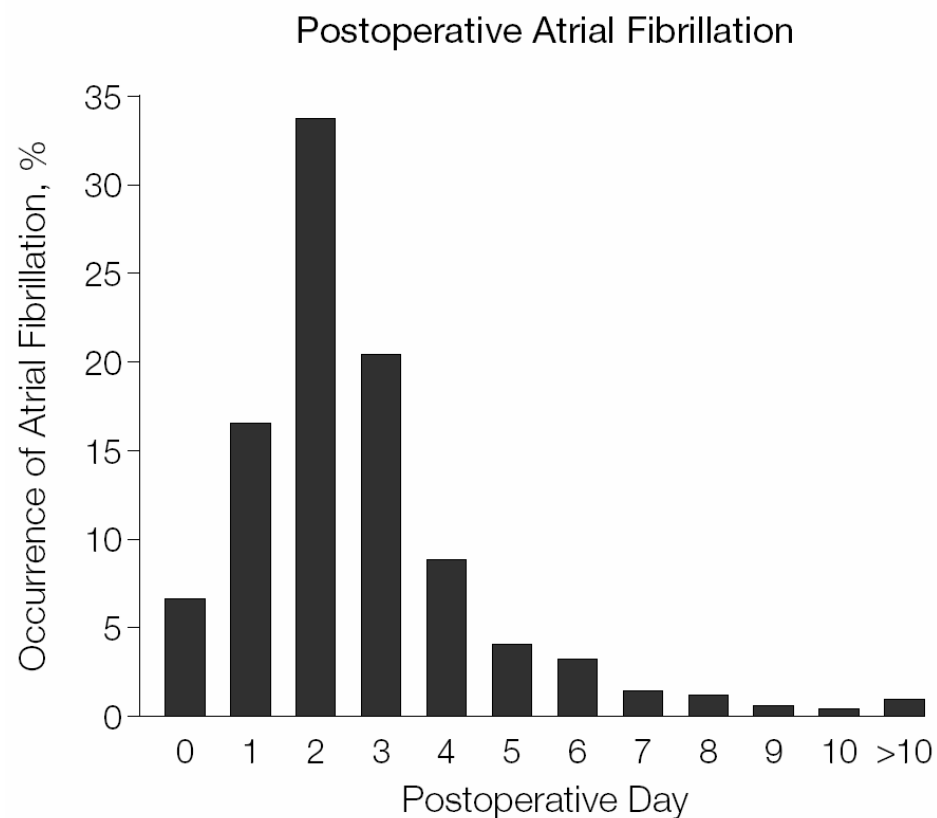
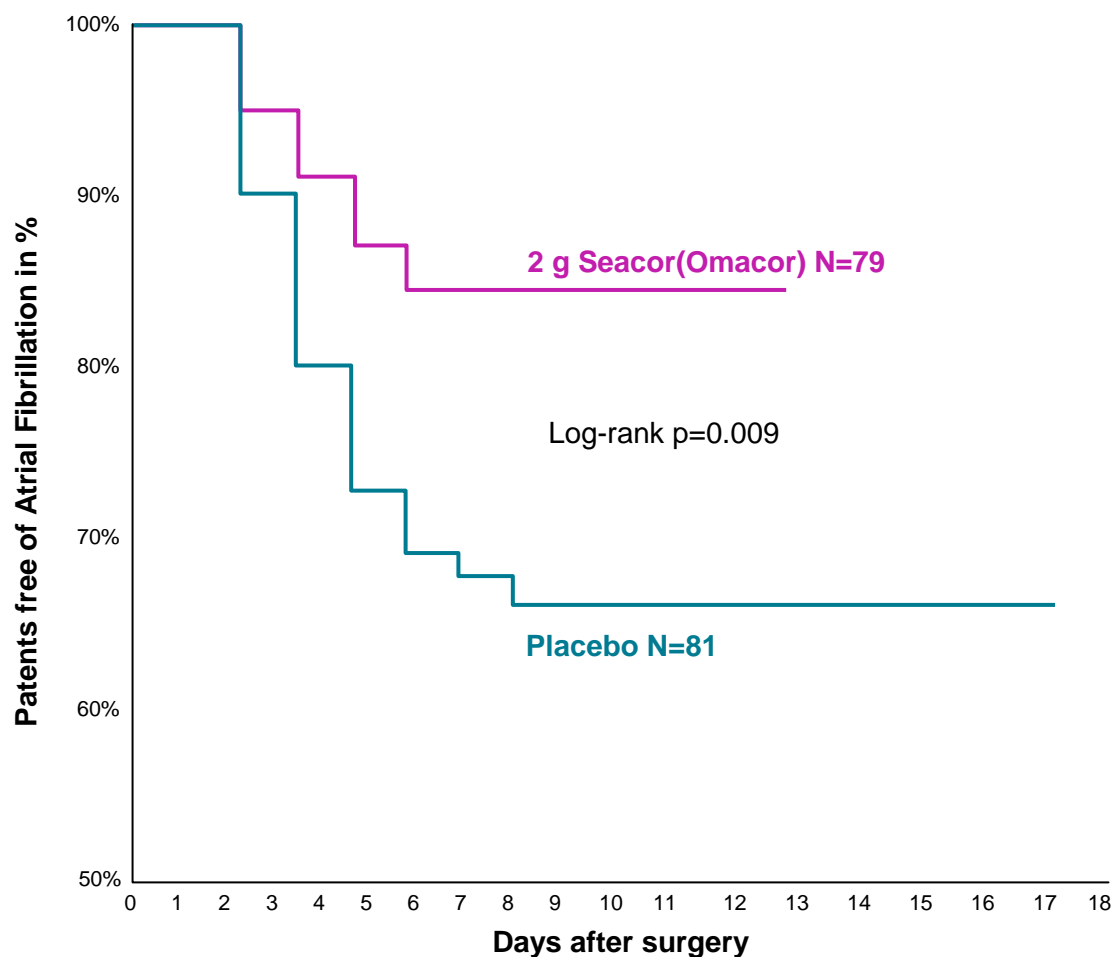
- **Epidemiological evidence of reduced incidence of AF with increased intake of EPA and DHA in 4815 elderly US adults**
- **GISSI-P showed 45% reduction in sudden death (which might be caused by cardiac arrhythmia)**
- **Animal data have shown that treatment with omega-3 fatty acids prevented arrhythmias**
- **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**

Mozzaffarian D Circulation 2004. GISSI-P Investigators, Lancet 1999. Pepe S, Circulation 2002. Calo L, J Am Coll Cardiol 2005. Leaf A, Circulation 2003. Christensen JH, Dan Med Bull 2003. Grimsgaard S, Am J Clin Nutr, 1998. Mori TA, Curr Atheroscler Rep 2004.

# Atrial fibrillation: Clinical results

Omacor reduceS incidence of post operative atrial fibrillation



15 May, 2008

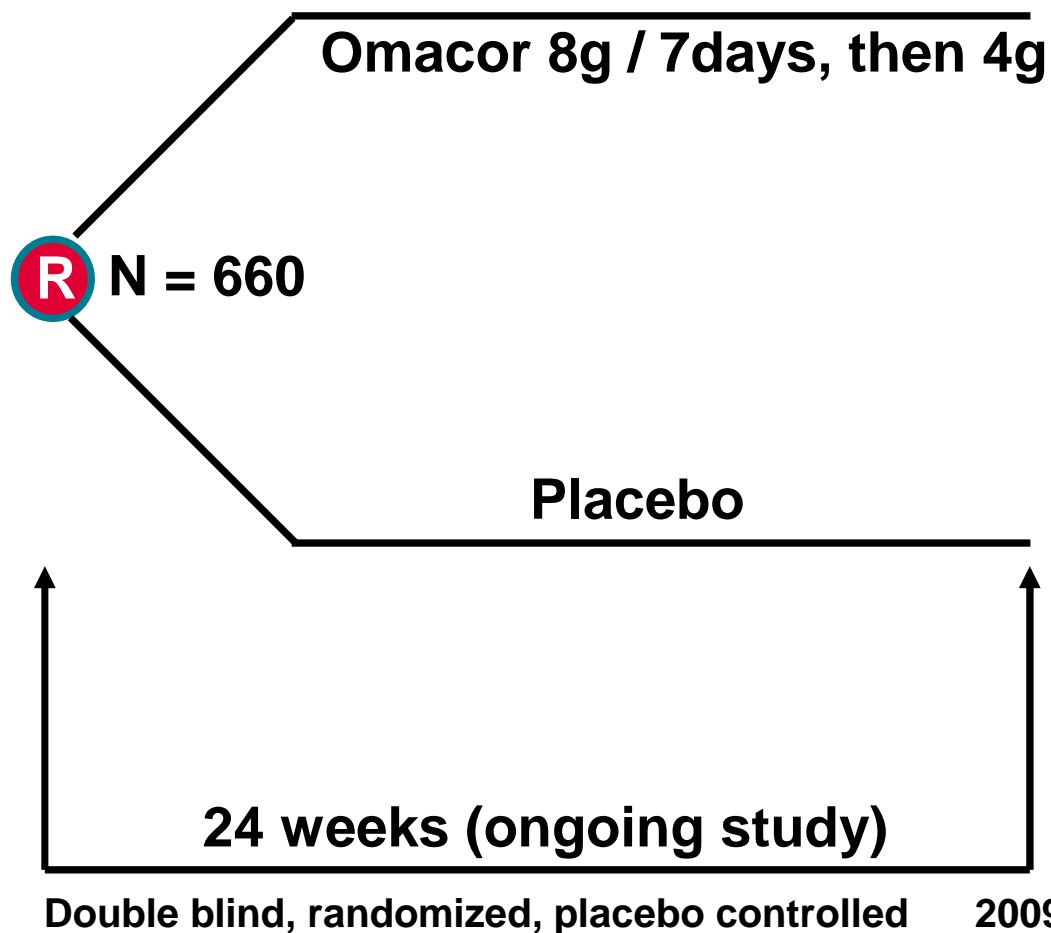
Note: 16  
Kaplan-Meier estimate of occurrence of postoperative atrial fibrillation in the study groups.  
Calo L et al, J Am Coll Cardiol 2005;45:1723-8

# Atrial fibrillation: OM8 (ongoing)

## Inclusion:

ECG evidence of paroxysmal or persistent atrial fibrillation.

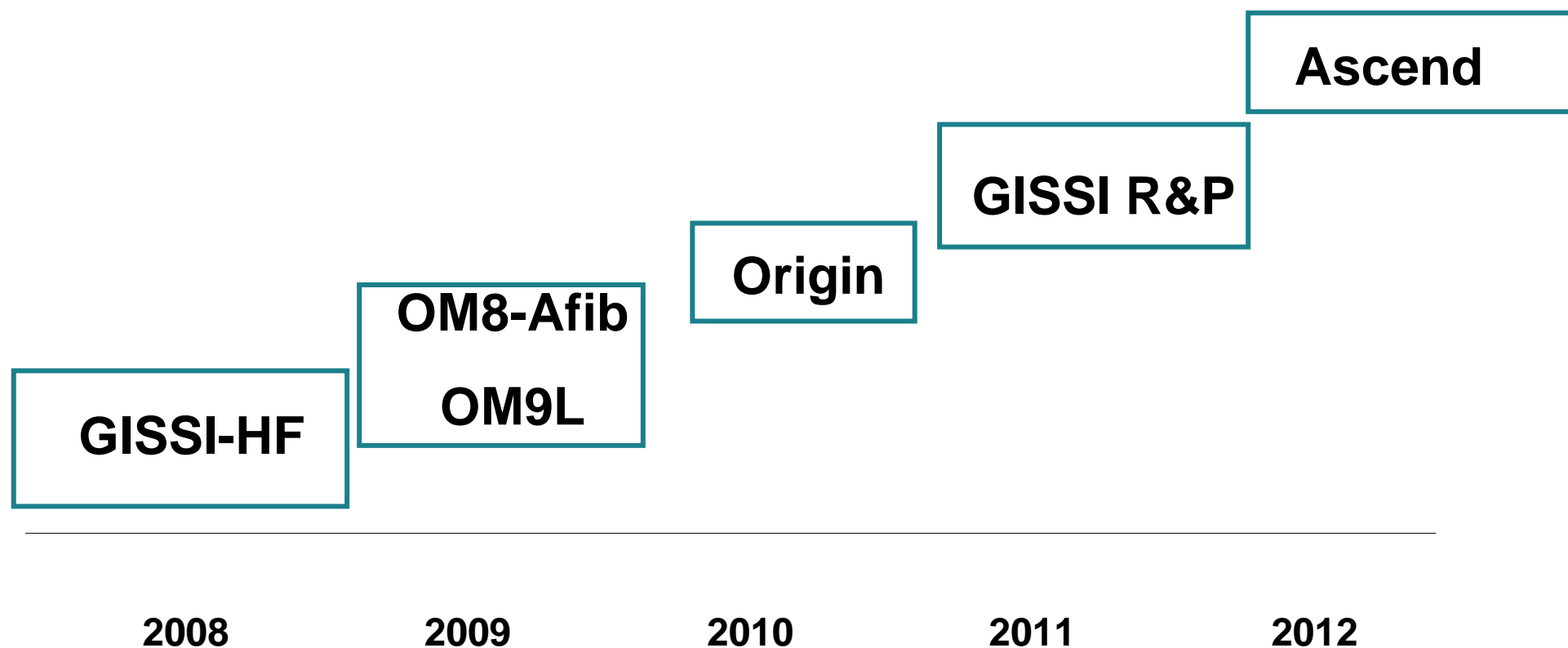
Older than 18 years



## Endpoint:

Prevention of atrial fibrillation relapse

# Selected future studies



Several interesting studies will report the next five years