OMEGA-3
What role do they play in treatment?

Omega-3 are **essential polyunsaturated fatty acids** contained in some foods and represented by alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (fig. 1).

Attention to omega-3 (ω-3) has increased over time, thanks to observations that have related the low mortality of Eskimos from heart disease to a diet rich in ω-3 fatty acids deriving from fish. Subsequent observational studies have confirmed a lower mortality rate from cardiovascular events in countries with the highest consumption of fish products, such as Japan.[1] This could be linked to the lower intake of saturated fats and to a better balance of polyunsaturated fats (fig. 1).

The cardiovascular protective mechanisms of ω-3 are not yet defined: antiarrhythmic, antithrombotic, antisclerotic effects are assumed, with improvement of the endothelial function and reduction in blood pressure.[2,3] The involvement of ω-3 (in particular eicosapentaenoic acid) in the synthesis of cytokines with antiinflammatory activity has also been taken into consideration.[2]

Recently, numerous food integrators rich in ω-3 have been marketed and ω-3-based pharmaceutical preparations have been produced. It is not known whether changing the ratio between saturated and unsaturated fats through a change in diet and taking ω-3 integrators without changing food habits have the same dietary meaning.[4]

This Information Package gives the results of the main trials that have assessed the efficacy, on clinically important outcomes, of a daily treatment with ω-3-based drugs.

On the following pages ...

The adjacent **figure 1** summarizes the classification of fats and fatty acids with the appropriate natural supply sources.

Besides ω-3, also part of the group of polyunsaturated fatty acids are ω-6, whose main component is linoleic acid.

On the other hand, ω-9 are monounsaturated fatty acids, of plant origin, represented in particular by oleic acid.

The dietary balance of the various components of this diagram may also vary greatly in relation to the eating habits of the various populations.

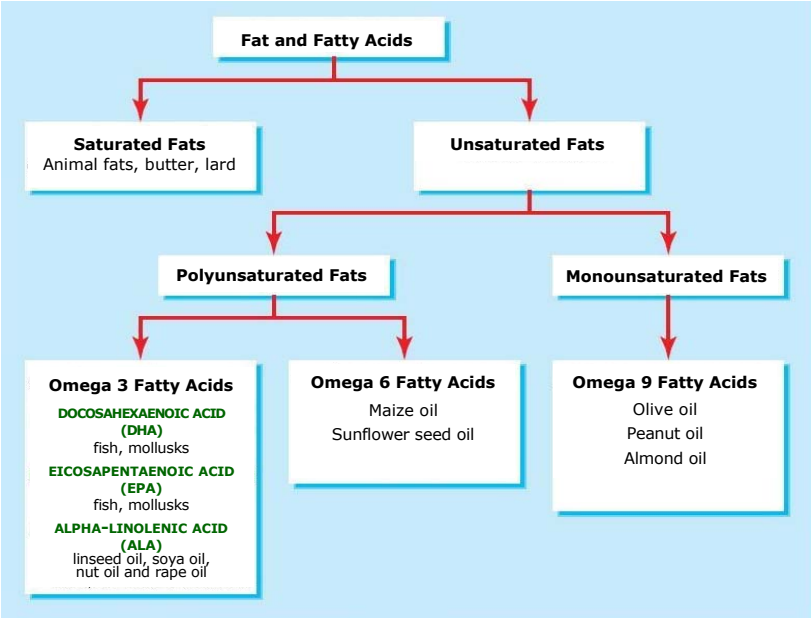

Figure 1. *Classification of fatty acids (modified by Din et al.[2])*

Omega-3 in CV prevention

OBSERVATIONAL STUDIES

Observational studies show that **eating fish once a week can reduce the risk of stroke and infarction** compared with someone who eats it less than once a month.[5, 6] These studies are, however, not enough to show the efficacy of ω-3: in fact, it is possible that persons who eat large amounts of these substances with their diet have a healthier life-style in general. Observational studies, however, are based on the assumption, then tested with RCT, that ω-3 have a role in cardiovascular prevention. [1,2]

RANDOMIZED TRIALS

A systematic review of the American **A**gency for **H**ealth Care **R**esearch and **Q**uality (AHRQ) of 2004 made an assessment of *randomized* trials (RCT) on the efficacy of diets rich in ω-3 or their intake in fixed daily doses (eg. through drugs) in primary and secondary cardiovascular prevention.[7] The same year the AHRQ also published a review of the effects of ω-3 on surrogate outcomes (including metabolic-type ones).[8]

PRIMARY PREVENTION
THERE IS STILL NO EVIDENCE

The AHRQ review[7] identified only one RCT in primary cardiovascular prevention.[9] This trial, that goes back to 1968 and involved 13,706 Norwegians, showed no preventive efficacy in the administration for one year of 5.5 g/day of linolenic acid (in the form of flax seed oil). It is possible that this is due to the fact that in that population the diet was already naturally rich in ω-3.

In the AHRQ review of the efficacy of ω-3 on the surrogate outcomes[8], it is found that at the dose of 3-4 g/day they reduce triglycerides by 10-30%. At the same doses, the variations of total cholesterol, HDL and LDL are not substantial.

IN PRACTICE...

in primary prevention, the efficacy of ω-3 on clinically important outcomes is not shown.
The reduction of blood triglycerides alone does not make it possible to establish the role of ω-3 in cardiovascular prevention.

SECONDARY PREVENTION
EFFICACY SHOWN WITH DRUGS

The AHRQ review[7] identified 11 RCTs in secondary prevention.
Six of these RCTs assessed the efficacy of **dietary advice** on a relatively limited number of patients (from 266 to 3114).
Three of these RCTs show results in favor of eating food containing ω-3 to reduce total and/or sudden mortality and major CV events. However, the largest of these trials provided contrasting results, showing an increase in cardiac deaths in patients with angina.[10]
The contrasting results and the methodological limitations of these trials (eg. type of action proposed based on simple dietary advice, lack of blindness and small sample size) do not allow definitive conclusions to be drawn on the efficacy of ω-3-rich diets.

Five RCTs assessed the efficacy of adding to the diet fixed daily doses of ω-3 (eg. with **pharmaceutical preparations**). Four of these trials had a small sample size (at most 300 patients), while the fifth is the GISSI-Prevention Trial, that assessed over 11,000 patients in 3.5 years.[11]

IN PRACTICE...

in secondary prevention, the best evidence available comes from the GISSI-Prevention Trial.

In primary prevention, AIFA note 13 considers the use of ω-3 exclusively in cases of family dyslipidemia.

The recommendations of AIFA note 13 for the use of ω-3 in secondary prevention are based on the results of the GISSI-Prevention Trial.

The GISSI-prevention trial

The aim of the GISSI-Prevention trial[11] was to assess the efficacy of administration of ω-3 (EPA + DHA at a ratio of 1:2) and/or Vitamin E in preventing cardiovascular events in patients with recent infarction.

GEOGRAPHICAL AREA	Italy (130 Cardiology Departments and 42 Rehabilitation Centers)
POPULATION (11.324 patients)	• **With infarction in the last 3 months** (on average, 25 days before) • No age limit (average: 59 years old) • On treatment with antiplatelet drugs (93%), ACE-inhibitors (47%), ß-blockers (44%), **hypolipemizing agents (5% at start and 46% at the end of the trial** OTHER FEATURES: 73% ate fish at least once a week 85% men, 36% with hypertension; 15% diabetics; 42% smokers Total Cholesterolemia: 210 mg/dl; triglyceridemia: 162 mg/dl

TRIAL "DESIGN" AND RESULTS

Comparing the patients who took **only ω-3** with those who took nothing, it emerges that **around 2 new events** (14.6-12.5 = 2.1) **were avoided every 100 patients treated in 3.5 years.**

11,324 patients with infarction in the last 3 months **randomized** with:

3.5 years

approx. 900 mg of ω 3 2836 patients	approx. 900 mg of ω 3 + 300 mg Vit.E 2830 patients	300 mg of Vit.E ω 3 2830 patients	Nothing 2828 patients

	ω-3	ω-3 + vit. E	vit. E	Nothing
Total mortality + non-fatal infarctions and strokes Comparison between each group	12.5%	12.7%	13.1%	14.6%
Comparison between those who take omega-3 and those who do not	12.6%		13.9%	

If the patients who took **ω-3 (with or without vit.E)** are taken and compared with those who do not take any **ω-3, every 100 patients treated, approximately one new event is avoided** (13.9 - 12.6= 1.3) **in 3.5 years.**

ω-3 EFFECTIVE IN POST-INFARCTION...

- ω-3 prevent around 1-2 new CV events in patients with recent infarction; on the other hand, vit. E has not been shown to be as effective: the differences between those who received vit. E and those who did not are not statistically significant, except that for cardiovascular deaths:
- the reduction in mortality and sudden deaths with ω-3 is already evident in the first 3-4 months; [12]
- ω-3 were not shown to be effective in preventing stroke;
- the results of the GISSI-Prevention Trial were obtained in a population where statins had been scarcely used (5% at the start and 46% at the end of the trial). This casts some doubt on the transferability of the results into current practice.

... and with STATINS?

Reassuring results on the efficacy of the association ω-3/statins appear to be obtained from an as yet unpublished RCT, presented in November, 2005 at the American Heart Association Congress. This trial shows that in 3664 patients treated in secondary prevention with statins at low doses (simvastatin 5 mg or pravastatin 10 mg), the addition of 1.8 g/day of ω-3 reduces by 2% the incidence of new coronary events after 4.5 years compared with treatment with statins alone (10.7% vs 8.7%).

Further information on Omega-3

EFFECTS ON HEART RATE: THE SUBJECT IS STILL OPEN TO DEBATE

- The GISSI-Prevention Trial showed a reduction in sudden deaths with fish oils already in the first 3-4 months of the trial;[12] this led to the assumption of an antiarrhythmic effect of the ω-3.

- A subsequent RCT[10], however, showed that in a group of 3114 patients with angina who were *recommended* to take an average of 2 portions of oily fish a week (or a similar amount of EPA in capsules), an increase in sudden deaths of 1.6% in 9 years occurred. However, this trial had clear methodological limits (like the type of action proposed - simple dietary advice - and lack of blindness).

- Another recent RCT[13] on 200 patients with an implanted defibrillator, monitored for around 2 years, showed that 1.8 g/day of ω-3 did not have a protective effect on the occurrence of arrhythmia compared to placebo. The trial, however, did not show an increase in mortality and/or episodes of ventricular fibrillation in patients treated with ω-3.

A wide-ranging debate is still in progress on the protective mechanisms of ω-3 on arrhythmic events: the most widely-held theory gives them a protective effect if the arrhythmia is the consequence of an acute ischemic episode.

INSUFFICIENT DATA IN OTHER DISEASES

Diabetes. A review by Cochrane in 2001 showed that there are no trials on the effects of ω-3 in diabetes that assess cardiovascular effects or overall mortality.[14] No further RCT published on the subject could be retrieved in Medline.

Asthma, arthritis and dementia. On these 3 subjects, the AHRQ published three systematic reviews between 2004 and 2005.[15-17] The 3 reviews showed that there are no conclusive data on the efficacy of administration of ω-3 in the prevention of clinical outcomes.

A glance at local prescription data: Modena

Women and men in comparison. The prescription of ω-3 was constantly increasing up until 2004; the reduction that is seen in 2005 is probably linked to the limitations introduced by AIFA note 13 on the use of ω-3 in primary prevention. The prescription is always higher in men than in women, probably in relation to the use of ω-3 in the secondary prevention of post-infarction.

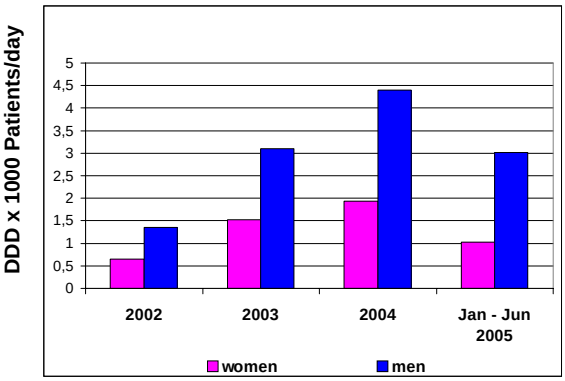

Figure 4: State of prescription of ω-3 (DDD 1000 patients/day) **in women and men,** from January, 2002 to June, 2005, at the Modena Local Health Care Trust.

Prescription by age range. With comparable numbers of possible patients, ω-3 are prescribed more between 50 and 80 year-old patients, perhaps in relation to the high prevalence of IMA in this age range. In 2005, a reduction in prescriptions is seen in all age ranges, as a result of the limitations of AIFA note 13.

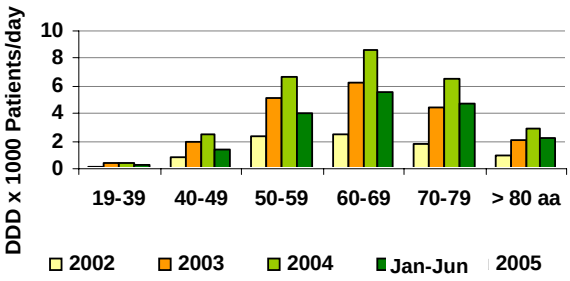

Figure 5. State of prescription of ω-3 (DDD 1000 patients/day) **by age range**, from January, 2002 to June, 2005, at the Modena Local Health Care Trust.

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Renato *Guttuso*. ***La Vucciria***, *1974. Oil on canvas, 300x300. Università degli Studi di Palermo (donated by the artist)*

ω-3 polyunsaturated fatty acids
Food recommendations

ω-3 polyunsaturated fatty acids are normally taken with food. The American Heart Association (AHA) has recommended eating food rich in ω-3 polyunsaturated fatty acids, to the extent of 2 grams a week. For people with heart disease, the advice is to take at least 1 gram of ω-3 a day.[1]

The so-called "oily fish" and some vegetables, such as nuts and soya, are the most important sources of ω-3 polyunsaturated fatty acids.

	To have 1 g of ω-3 you must eat		To have 1 g of ω-3 you must eat
Fresh anchovies, sardines	40 g	Sole	180 g
Fresh salmon	42 - 70 g	Fresh tuna	70 - 300 g
Herring	50 g	Tinned tuna	200 - 350 g
Grey mullet	75 g	Cod	400 g
Smoked salmon	48 - 80 g	Squid, crayfish	220 - 250 g
Fresh mackerel	50 g	Mussels	280 - 330 g
Rainbow trout	110 g	Catfish	550 g
Halibut	100 g	Potted eel	absent
Tinned sardines in oil	90 g	Soya	70 g
Gilthead	160 g	Nuts	16 g

Contents of ω-3 fatty acids in some fresh and tinned foods. *(Am. Heart Assoc. 2002[1] and Food Composition Tables of the Nat. Food and Nutrition Res. Instit. 2000, form. [18])*

Several studies have shown that preservation and preparation methods may have major effects on the amount of ω-3 fatty acids actually present in food.

- The **preservation** procedures reduce the content of ω-3 in a variable way: smoking and salting may reduce them by half, while freezing reduces them to a lesser degree (from 10 to 20%).

  Tinned fish (tuna, mackerel, sardines) undergo various procedures (cooking, salting, etc.) that reduce their content of ω-3 fatty acids, but with notable differences (from 10 to 50% less than the fresh product) depending on the production company. It must be remembered that food preserved in salt can provide large and undesirable quantities of sodium.
- **Rapid cooking** (no longer than 15-20 minutes) under steam, in a bag, on a plate, in a pan with very little oil or in the oven (even a microwave) does not change to any great extent the ω-3 content of fish. On the other hand, **deep-fat frying** (in a large amount of cooking oil, such as in the deep-fryer) reduces the ratio between the ω-3 and the other lipids by even as much as 20 times or more.
- Eating **vegetables** is a bench mark of how to behave correctly in matters of eating; however, the fibres contained in them can reduce the absorption of various lipids. Because of this possible interference, it is better to eat fish with limited amounts of green vegetables.
- The problem of accumulation of heavy metals in salt-water fish is one that is facing us today. Women of child-bearing age and **pregnant women** are recommended not to eat too much sea-bass, swordfish and shark, for the reason that, because these fish feed in the depths of the sea, they appear to be most exposed to mercury contamination.