European Heart Journal Supplements (2020) **22** (Supplement J), J49–J53
The Heart of the Matter
doi:10.1093/eurheartj/suaa118

ESC
European Society
of Cardiology

The journey of omega-3 fatty acids in cardiovascular medicine

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KEYWORDS
Omega-3 acid ethyl esters;
n-3 PUFA;
Secondary prevention after myocardial infarction

In subjects with cardiovascular risk factors or in patients in need of secondary prevention, hypertriglyceridemia is a well-defined risk factor for adverse cardiac events. Drugs containing n-3 polyunsaturated fatty acids (*n-3 PUFAs*) are approved for treatment of hypertriglyceridemia. In 1999, a cardioprotective effect in post infarct patients was suggested by a large multicentre study, the GISSI prevention trial. The hypothesized mechanism of action was an antiarrhythmic action leading to reduction of the sudden death. However, such a cardioprotective effect of n-3 PUFAs has not been straightforward like for other cardiovascular drugs such as aspirin, statins or ACE inhibitors. On the contrary, it has been a long journey with several ups and downs. Recently, the European Medicines Agency (EMA) has not confirmed the risk benefit of low dose of n-3 PUFA in preventing outcomes after a myocardial infarction. Since the EMA decision, the use of a high dose (*4g daily*) of pure and stable EPA in a multicentre, international trial, the REDUCE-IT study showed a clear cardiovascular event reduction which was not confirmed in another trial, the STRENGTH study, which utilized 4g daily of an EPA+DHA mixture. It follows that the OMEGA-3 fatty acid story seems to be endless and the last word on cardiovascular benefits cannot be pronounced. We report a brief narrative of an entire journey from the beginning to nowadays.

Premise

Drugs containing omega-3 fatty acid ethyl esters also termed n-3 polyunsaturated fatty acids (n-3 PUFA) have been approved in the majority of the European Union member states for the treatment of hypertriglyceridaemia. Their development, however, has not been straightforward like other cardiovascular drugs and can be summarized as a long journey with several ups and downs. Recently, the European Medicines Agency confirmed that low-dose omega-3 fatty acids are not effective in preventing further problems with the heart and blood vessels in patients who have had a heart attack. A brief description of this journey is the scope of the present report.

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The beginning: *ups*

Attention on the effectiveness of n-3 PUFA began to take shape with some observational studies related to high fish consumption. In 1985, Kromhout *et al.*[1] were the first to document in a Western country, the Netherlands, that more than one meal of fatty fish per week reduces mortality by 50%. Several other studies followed, all coming to the conclusion that a regular consumption of fish oil once, twice or more a week is associated with lower risk of death from cardiovascular disease (CVD). Of course, observational studies and retrospective analyses have several limitations, especially when dietary factors are involved. These studies, however, prompted the interest of the scientific community to properly assess whether n-3 PUFA, found in fish and other seafood, are cardioprotective.

It is from this background that the idea of the GISSI-Prevenzione study (GISSI-P) came about. GISSI-P is a study

on 11 324 patients surviving recent myocardial infarction (MI) randomly assigned to receive n-3 PUFA with a content of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) not lower than 85% with an average ratio EPA/DHA 1:2. The study had four arms: n-3 PUFA (1 g daily, $n = 2836$ daily); vitamin E (300 mg daily, $n = 2830$), both ($n = 2830$), or none (control, $n = 2828$) for 3.5 years.[2] The results showed a significant 10% relative decrease (by two-way analysis) in the risk of the combined primary endpoint of death, non-fatal MI, and non-fatal stroke. There was also a 17% relative decrease in CV death, by two-way analysis. Vitamin E failed to show any improvement. The positive effects on n-3 PUFA occurred early after the beginning of the treatment and were interpreted as a prevention of sudden death.

Actually, the antiarrhythmic effect of n-3 PUFA is not new, suggested as early as in 1976 and later demonstrated in several animal models.[3] n-3 PUFA seem to stabilize the electrical activity of myocytes by elevating the action potential threshold, shortening its duration, and prolonging the relative refractory time.[4] This is attributable to the modulation of the ion channel conductance of the sarcolemma, through the inhibition of the voltage-dependent Na^+ currents and of L-type Ca^{2+} currents.[4]

Based on these positive results of the GISSI-P, n-3 PUFA were authorized to enter the market in the European Union in 2001 with several commercial trade names. In agreement with this hypothesis, a meta-analysis of three double-blind, randomized, placebo-controlled intervention studies involving 1148 patients with implantable cardioverter-defibrillators (ICD) suggested that patients with coronary artery disease (CAD) might benefit from the supplementation with n-3 PUFA preventing ICD discharges.[5]

The continuation: *downs*

Later on, the GISSI-P trial was criticized because of its PROBE design and it was questioned whether the results were relevant in the context of more contemporary standard of care for MI which has substantially evolved since the time of the GISSI-P. Of course, in 1999, in the absence of primary angioplasty, the phenotype of MI was different from the one of today and secondary prevention treatment was not optimal. This argument, however, should be applied to all the other secondary prevention drugs such as the beta-blockers.[6] The PROBE design, which is used in several multicentre trials, has the advantage of being closer to 'standard-real world' practice and the hard endpoints evaluated in the GISSI-P trial are unlikely to be influenced by the probe design. Marchioli *et al.*[7] re-analysed the GISSI-P database to investigate the validity of the results in view of the changed and modern therapy of post-MI patients. No interaction was found with any of the contemporary drugs, including statins.

Nevertheless, 10 years later, with the aim to verify the results of the GISSI-P study, another trial named OMEGA study was conducted in 104 centres in Germany to test the effects of 'Pharma Grade' n-3 PUFAs (1 g/day for 1 year) on the rate of sudden cardiac death in survivors of acute MI.[8] Secondary endpoints were total mortality, major adverse cerebrovascular and CV events. The important difference between GISSI-P and OMEGA relies on the background therapy. In the OMEGA trial, primary coronary angiography was performed in 93.8% of patients and all received state of art cardioprotective drugs, including lipid-lowering therapy. The rate of sudden cardiac death during follow-up was 1.5% with no difference among groups. There was no difference in the secondary endpoints or in the rate of major CV or cerebrovascular events. The study, however, was described by the authors as underpowered and, actually, it was underpowered. At the end, it had only 44% power to prove 45% risk reduction of sudden cardiac death and only 19% to test the most realistic, in view of the high percentage of primary angioplasty, risk reduction of 25% that would require more than 20 000 patients instead of the 3851 enrolled. There are other issues to take into consideration. For instance, in both study groups self-reported fish consumption increased significantly during the trial, which may have contributed to the low event rate and may have attenuated a possible beneficial effect of the study drug. Therefore, the OMEGA trial shows the important progress of cardiology in treating MI with primary angioplasty and the relevance of guideline-recommended treatment of post-infarction patients. As the trial does not fulfil statistical (and regulatory) principles, it is difficult to make any comment whether omega-3 therapy, in adjunct to the other post-MI drugs, is redundant or not.

The journey continues

Three retrospective cohort studies on 28 439 post-infarction patients receiving contemporary 'real world' therapy tested the effects of n-3 PUFA patients, confirming a highly significant reduction of mortality.[9–11] This also certifies that contemporary treatment does not disqualify the benefits of n-3 PUFA.

The same research group of GISSI-P designed another study, but this time on heart failure (HF) patients: the GISSI-HF. One gram daily of n-3 PUFA provided a small beneficial advantage in terms of mortality and hospital admission for CV reasons in patients with symptomatic HF of any cause and with any level of ventricular ejection fraction, already treated with the recommended therapies available at the time.[12] Even in this case, the greatest proportion of the absolute risk reduction on total mortality was attributed to the reduction of arrhythmic death.[12]

Thereafter, several other important trials were conducted, evaluating the effects of n-3 PUFA in a rather heterogeneous setting of patients. The most relevant are the ORIGIN trial[13] which evaluated the effects of 1 g daily of n-3 PUFA in a very mixed diabetic population (12 536 patients) receiving primary prevention medication. The overall results were neutral. The SU.FOL.OM3 trial[14] randomized 2501 French patients with history of MI, unstable angina, or ischaemic stroke to 600 mg daily of n-3 PUFA or placebo. Again, the overall results were neutral. The R&P trial investigated the effects of 1 g daily of n-3 PUFA or placebo on 12 513 patients at risk for CV disease without acute MI.[15] The overall results were also neutral. Thus, all these

prospective studies with the exception of GISSI-P and GISSI-HF, failed to show a clear benefit of n-3 PUFA. Three large retrospective trials, with all the cautions that apply to retrospective analysis, however, demonstrated a benefit. It was recognized that the heterogeneity of the population involved in the prospective trials and the different doses of n-3 PUFA used could have contributed to the neutral results. Nevertheless, a certain scepticism started to grow among the scientific community on whether the n-3 PUFA could be useful or not in patients after MI.

The journey evolves into meta-analyses

At this stage, in the hope to provide some light on whether n-3 PUFA should be used in secondary prevention, several meta-analyses on the main randomized clinical trials involving large numbers of patients have been performed,[16] including a Cochrane systematic review.[17] The results were inconclusive, with some meta-analyses being positive, others negative. Of course, the results of a meta-analysis highly depend on the included studies which, in turn, depend on the definition of both the population and, in case of n-3 PUFA, the type of n-3 PUFA used, a rather difficult task considering the nature of n-3 PUFA which can be considered a drug or a food supplement. A typical example is the meta-analysis of Aung's and Maki's[18,19] which found an identical relative risk for cardiac death (0.973) but, due to a difference in the selection of chosen studies, the confidence interval (CI) in the first meta-analysis was not significant while in the second one reached significance.

It is therefore of the highest importance, when performing a meta-analysis, to make sure that only the studies that are relevant to answer the specific questions are considered and evaluated.

Even the Cochrane meta-analysis, which is based on all data, does not provide the final answer on the omega-3 question.[17]

Despite all this, in 2018 two further studies were conducted: the ASCEND and the VITAL trials.

ASCEND is a randomized trial assessing whether 100 mg daily aspirin safely prevents CVD and cancer in patients with diabetes without known arterial disease. At the same time, it investigated whether supplementation with 1 g n-3 PUFA daily prevents CVD.[20]

The primary endpoint of a first serious vascular event was not significantly different between 1 g n-3 PUFA and placebo after a mean follow-up of 7.4 years (rate ratio 0.97, 95% CI 0.87–1.08; $P = 0.55$). There was also no difference in death from any cause between the 1 g n-3 PUFA group and placebo. Among patients with diabetes but without evidence of CVD, in the n-3 PUFA group there was a trend towards a reduced rate of death from any cause, in comparison to the placebo group, with death reported in 752 patients (9.7%) and 788 patients (10.2%), respectively (rate ratio 0.95, 95% CI 0.86–1.05). Moreover, additional subgroup analysis showed that there were significantly fewer vascular deaths in the n-3 PUFA groups than in the placebo group [196 patients (2.5%) vs. 240 (3.1%)] [rate ratio (95% CI) 0.82 (0.68–0.98)].

The VITAL trial examined the effects of omega-3 fish oil supplementation (1 g/day containing 460 mg EPA and 380 mg DHA) with or without 2000 IU/day vitamin D for a median of 5.3 years.[21] The study population consisted of 25 871 men aged 50 and older and women aged 55 and older with no previous heart attacks, strokes, or cancer. The primary endpoints of major cardiovascular events (composite of MI, stroke, and death from CV causes) and invasive cancer of any type were not significantly different between 1 g n-3 PUFA and placebo (hazard ratio 0.92, 95% CI 0.80–1.06; $P = 0.24$ for major CV events; and hazard ratio 1.03, 95% CI 0.93–1.13; $P = 0.56$ for invasive cancer). Participants taking omega-3 treatment did experience a statistically significant 28% reduction in total MI rate (including a 40% reduction among those who consumed <1.5 servings of fish per week). Omega-3-treated group had significant reductions in rates of fatal MI, total coronary heart disease, and percutaneous coronary intervention. No significant reductions in stroke and death rates from CV causes were observed. So, once again, no real conclusive answer from the meta-analyses or the last trials.

The journey ends with 'REDUCE-IT'

Indeed, this rather long and complicated journey ends with the results of the REDUCE-IT trial.[22]

REDUCE-IT is a multicentre, randomized, double-blind, placebo-controlled trial, involving patients with established CVD or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135–499 mg/dL and LDL cholesterol of 41–100 mg/dL. A total of 8179 patients were enrolled (70% were secondary prevention of CV events and 30% high-risk primary prevention, with diabetes and one additional risk factor) and followed for a median of 4.9 years.

The patients were randomly assigned to receive 2 g of icosapent ethyl (EPA) twice daily (4 g daily in total) or placebo.

The primary endpoint was a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina. The key secondary endpoint was a composite of CV death, non-fatal MI, or non-fatal stroke.

The study showed that purified n-3 PUFA reduced the primary endpoint by 25% and the secondary endpoint by 26%.

A primary endpoint event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22% of the patients in the placebo group (hazard ratio 0.75, 95% CI 0.68–0.83; $P < 0.001$); the corresponding rates of the key secondary endpoint were 11.2% and 14.8% (hazard ratio 0.74, 95% CI 0.65–0.83; $P < 0.001$). The study was powered for a 15% hazard ratio reduction, instead a reduction of 25% was achieved.

The rates of secondary efficacy endpoints, as assessed according to a pre-specified hierarchical schema, were also significantly lower in the treated group than in the placebo group, including the rate of CV death (4.3% vs. 5.2%; hazard ratio 0.80, 95% CI 0.66–0.98; $P = 0.03$).

The authors observed that the CV benefits were similar across baseline levels of triglycerides (<150, ≥ 150 to <200, and ≥ 200 mg/dL). In addition, the significantly

lower risk of major adverse CV events in the treated group than in the placebo group appeared to occur irrespective of the triglyceride level at 1 year ($\geq$150 or $<$150 mg/dL), suggesting that the CV risk reduction was not associated with triglyceride level reduction and suggesting that the benefits should be explained by metabolic effects other than a reduction of triglyceride level. As expected, there were no haemodynamic effects induced by treatment. Contrary to what found in the GISSI studies, the timing of the divergence of the Kaplan–Meier curves show a delayed onset of benefits, which may reflect the time needed for a benefit from a positive metabolic action or may indicate that other mechanisms are involved. The modestly higher rate of bleeding events in treated groups suggests there may be an anti-thrombotic mechanism of action, although it is unlikely that an anti-thrombotic effect would reduce the rate of elective revascularization. In addition, if the full explanation involved an anti-platelet or anti-coagulant effect, one might expect a large increase in the rate of major bleeding events, which was not observed.[19]

Stabilization, reduction of progression, or even regression of coronary plaque may also have played a role. This is also supported by the lower rates of cardiac arrest and sudden cardiac death of treated groups that, in a way, is in line with the early findings of GISSI-P and GISSI-HF. Another hypothesis is an anti-inflammatory action, in line with the difference in high sensitivity C-reactive protein level in favour of the treated group. Blood samples, obtained during the conduct of the trial, have been obtained and stored for biomarker and genetic analyses and, hopefully, will answer which of the current hypotheses is the right one. There are other ongoing trials with different doses of EPA in secondary prevention, the results of which should be available soon.

Final thoughts

The story of n-3 PUFA and now also of eicosapentaenoic acid ethyl esters is a long story starting almost 40 years ago and still ongoing, although it seems to have reached a happy ending. It is an important journey considering the nature of n-3 PUFA which are agents devoid of any large haemodynamic effects, but acting primarily by modifying the metabolism and, possibly, the intrinsic structure of the myocardium, i.e. the cardiac membranes. Therefore, it is a different approach from that of the more classical secondary prevention drugs. What is surprising is that, in all these years, no dose–response studies have been performed and, maybe, that the difference between the old (often with modest or uncertain action) and the new (with clear effect) studies is related to the dosage: 4 g/day in REDUCE-IT vs. 1 g/day in the GISSI's. In addition to dose, the compound or product utilized may also play a role in cardiovascular risk reduction. The moderate to high doses of pure EPA utilized in both the Japan EPA Lipid Intervention Study (JELIS) ($\sim$2 g/day) and REDUCE-IT (4 g/day) cardiovascular outcome trials led to the attainment of the primary cardiovascular endpoint and thus cardiovascular event reduction.[22,23] However, the high dose (4 g/day) of an EPA and DHA free fatty acid mixture utilized in the Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridaemia (STRENGTH) had a low probability of showing cardiovascular benefit and the trial was stopped for futility in January of 2020 based on the recommendation from an independent data monitoring committee.[24] Therefore, the last word on the benefits of omega-3 fatty acids cannot be pronounced.

The omega-3 fatty acid story is an interesting story as it did evolve with the evolving of therapy for CAD, a journey not necessarily available for other classes of drugs. This issue of the *European Heart Journal* supplement is focused primarily on the new achievements, but we thought it was fair and interesting to remember where the story comes from.

Funding

This work was supported by a grant from Fondazione Anna Maria Sechi per il Cuore (FASC), Italy. The funders had no role in the study design, data collection and analysis, decision to publish, or the preparation of the manuscript. This paper was published as part of a supplement supported by an unrestricted educational grant from Amarin Pharma, Inc.

Conflict of interest: none declared.

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