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# Clinical results and mechanism of action of icosapent ethyl

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Serum triglyceride concentration is considered as an additional component that often contributes to residual cardiovascular risk in patients already at high risk; these considerations have led to several clinical studies aimed at evaluating the efficacy of supplements based on omega-3 fatty acids in reducing serum triglyceride levels and consequently cardiovascular risk. Although partially inconclusive and contradictory, these clinical trials laid the foundations for the implementation of the REDUCE-IT and EVAPORATE studies, in which the use of a purified derivative of eicosapentaenoic acid, icosapent ethyl, resulted in a significant reduction both of the composite for cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke and of the reduction in the volumetric progression up to the induction of a real regression of the coronary atheromatous plaques detected by computerized coronary angiography tomography. Surprisingly, these brilliant results seem to be, at least in part, not related to the reduction of triglyceride concentration. The purpose of this article is to examine the latest evidence regarding icosapent ethyl therapy, describing the results of the main clinical trials performed to date and formulating hypotheses on the potential mechanisms of action of this fascinating molecule.

## Introduction

Despite the significant progress in terms of early diagnosis and the discovery of innovative effective therapies in order to reduce the risk of cardiovascular diseases, the latter still represents the main cause of morbidity and mortality in the world today. According to the data collected by the Global Burden of Disease Study 2019, from 1990 to 2019, the prevalence of cardiovascular diseases has increased from 271 million to 523 million, and the number of deaths related to the same cause increased from 12.1 million to 18.6 million.[1] Among the known and modifiable risk factors in patients in primary and secondary prevention, we find low-density lipoprotein (LDL) cholesterol (LDL-C), a key target of the majority of available lipid-lowering therapies, where the inhibitors of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase represent the first line of therapy in the majority of cases. In addition to these therapies, eminently aimed at reducing LDL-C values, although essential in the therapeutic armamentarium dedicated to risk reduction, there is an ever-growing need to identify further therapeutic targets that contribute to fuelling the persistence of a residual cardiovascular risk; this is particularly important in patients undergoing secondary prevention, in order to optimize and reduce the possibility of a second event. Recently, an innovative therapy based on a purified extract of eicosapentaenoic acid, created for patients with hypertriglyceridaemia and a high cardiovascular risk, seems to respond at least partially to this pressing need.

## Triglycerides, omega-3 fatty acids, and cardiovascular risk: the first evidence

Triglycerides, originally considered as 'non-protagonists' in cardiovascular risk, have also recently returned to the centre of attention: in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) study, it emerged that in secondary prevention patients taking statin

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therapy, a reduction in triglyceride concentration below 150 mg/dL was associated with a lower risk of ischaemic coronary artery disease, regardless of the LDL-C value: in particular, for each reduction of 10 mg/dL in triglyceride concentration, there was a 1.6% reduction in the composite endpoint ($P < 0.001$).[2] Subsequently, several clinical studies investigated the possible efficacy in reducing cardiovascular risk through the use of a therapy aimed at reducing triglyceride levels through the use of omega-3 fatty acids: the Italian study Italian Group for the Study of Survival in Myocardial Infarction (GISSI-Prevenzione) through the use of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with a ratio of 1:2; the VITAmin D and OmegA-3 TriaL (VITAL) and A Study of Cardiovascular Events in Diabetes (ASCEND) studies, where the combination of EPA and DHA was used with a fixed ratio of 1:3. Different results emerged from these clinical studies: in the GISSI-Prevention, it was demonstrated that, at 3.5 years, therapy with EPA and DHA in patients with recent myocardial infarction allowed to obtain a reduction in the risk of the primary composite endpoint of death, non-fatal myocardial infarction, or non-fatal stroke [relative risk (RR) 0.90, 95% confidence interval (CI): 0.82–0.99]; on the other hand, in the ASCEND and VITAL trials, omega-3 fatty acid supplementation in a population of diabetic and non-diabetic patients, respectively, in the context of primary prevention, did not demonstrate a significant reduction in the primary ischaemic composite endpoint.[3] In the Japan Lipid Intervention Study (JELIS), 18 645 patients with a total cholesterol value ≥ 6.5 mmol/L were randomized to receive pravastatin or pravastatin plus 1.8 g of EPA; at the 5-year follow-up, a significant reduction in the primary composite endpoint of major coronary events was observed in the group of patients receiving EPA [hazard ratio (HR) 0.81, 95% CI: 0.69–0.95; $P = 0.01$], in both primary and secondary prevention patients.[3] On the contrary, in the multicentre, randomized, double-blind study, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH), the efficacy of the administration of a formulation of EPA and DHA vs. oil was evaluated of corn seeds on the reduction of cardiovascular risk in a population of 13 078 patients with hypertriglyceridaemia and a high cardiovascular risk; the primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, and unstable angina. The results of the study, which was interrupted early due to the low probability of clinical benefit, did not demonstrate significant differences between the two study arms.[4] Finally, the two multicentre, placebo-controlled, randomized, and double-blind studies, Multi-centre, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension (MARINE) and effect of AMR101 on Triglyceride Levels in Patients on Statins With High Triglyceride Levels (ANCHOR) demonstrated that icosapent ethyl (IPE), a stable ethyl ester of eicosapentaenoic acid, was effective and with a safety profile comparable to placebo in reducing triglyceride values in a patient population with hypertriglyceridaemia; however, cardiovascular outcomes were not analysed in these studies.[5]

This mass of scientific evidence, although indicative of the potential in terms of reducing cardiovascular risk associated with the use of EPA derivatives, was still not very homogeneous, partially inconclusive and at times contradictory; for these reasons, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT6) study was designed.

## The REDUCE-IT study

In the multicentre, prospective, randomized double-blind and placebo-controlled REDUCE-IT study, the efficacy of IPE in reducing the risk of cardiovascular events was investigated in a population of 8179 patients with fasting triglyceride values between 135 and 499 mg/dL and known cardiovascular disease, or with diabetes mellitus and at least one additional cardiovascular risk factor, already on statin therapy. The primary endpoint was the composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina. Key secondary endpoints were the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Administration of IPE 4 g/day reduced the relative risk by 25% for the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina compared with placebo. In particular, the primary endpoint occurred in 17.2% of subjects receiving IPE and in 22.0% of patients in the placebo group (HR: 0.75; 95% CI: 0.68–0.83; $P < 0.001$), with a number needed to treat (NNT) to prevent a primary endpoint of 21 (95% CI: 15–33). Death from all causes, non-fatal myocardial infarction, and non-fatal stroke were also lower in the group of patients treated with IPE than in the group treated with placebo (13.4% vs. 16.9%; HR: 0.77; CI: 0.69–0.86; $P < 0.001$).[5,6] All patients enrolled in the study had been on statin therapy for at least 4 weeks, with an LDL-C concentration ranging between 41 and 100 mg/dL. One year after the start of treatment, the benefits obtained on cardiovascular risk proved to be independent of both the starting triglyceride levels and the basal triglyceride levels at the time of starting the therapy.[2] These benefits have been shown to be consistent across a wide variety of settings[7]: in the REDUCE-IT REVASC study, the incidence of needing percutaneous coronary revascularization (PCI) or coronary artery bypass graft (CABG) was reduced by 34% in patients treated with IPE compared with patients treated with placebo (9.2% vs. 13.3%; HR: 0.66; CI: 0.58–0.76; $P < 0.0001$); in REDUCE-IT DIABETES, the incidence of the primary endpoint decreased from 22.4% to 18.1% (HR: 0.77; 95% CI: 0.68–0.87) in patients treated with IPE compared to placebo; in REDUCE-IT CABG, the primary composite endpoint in patients with a history of prior CABG decreased by 24% in the IPE-treated group compared to the placebo group (HR 0.76; 95% CI: 0.63–0.92; $P = 0.004$); finally, in REDUCE-IT RENAL, it was demonstrated that the benefits of IPE on the reduction of fatal and non-fatal ischaemic events are maintained independently of the glomerular filtration rate (eGFR).

## The EVAPORATE study

Following the evidence of an important reduction in cardiovascular events mediated by the intake of IPE, numerous theories have been elaborated which hypothesize how

the beneficial properties on cardiovascular risk of this molecule must necessarily be mediated by other pathways which do not see the sole protagonist mere reduction in the concentration of serum triglycerides. The multicentre, randomized, double-blind, and placebo-controlled study, Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE8), was born with the idea of evaluating whether the addition of 4 g/day of IPE, in addition to diet and statin therapy, may trigger a volume reduction of coronary atheromatous plaques (causing one or more stenoses ≥20%) detected by coronary computed tomography angiography (CCTA) in patients with fasting hypertriglyceridaemia. At 18 months from the beginning of the study, a significant reduction in the volume of low attenuation plaques (LAP) of 17% was observed in the IPE therapy group, but not only in the placebo therapy group, there was an increased volumetrics of LAP plaques by 109% ($P = 0.0061$).

The mechanism of action of IPE and current hypotheses is beyond the reduction of triglycerides (*Table 1*).

The benefits observed from the use of IPE in the REDUCE-IT study would appear to be, at least in part, due to pleiotropic effects that go beyond triglyceride reduction; this is because the extent of the reduction in cardiovascular risk obtained in patients treated with IPE does not seem to vary in proportion to the reduction in triglyceride concentration obtained following the start of treatment.[8] We list below the potential mechanisms involved in the reduction of cardiovascular risk observed in the different trials.

Antiplatelet aggregation effect IPE is a stable ethyl ester of eicosapentaenoic acid, an omega-3 fatty acid. EPA is an enzymatic precursor for the formation of thromboxane A3 (with a neutral effect on platelet aggregation) and for the formation of prostaglandin I3 (with an inhibitory effect on platelet aggregation). If ingested in quantities ≥4 g/day, EPA would appear to determine a greater synthesis of prostaglandin I2, enhancing the inhibition effect of platelet aggregation.[3] Indeed, the major bleeding rates observed in the REDUCE-IT study population receiving IPE were more frequent than in the placebo group (2.7% vs. 2.1%, $P = 0.06$), albeit in the absence of fatal bleeding events. However, the rates of haemorrhagic stroke and gastrointestinal haemorrhage were not different in the two groups.[8]

**Table 1** Potential mechanisms of action of icosapent ethyl in cardiovascular prevention

1. Reduction of circulating triglyceride levels
2. Antiplatelet aggregation effect
3. Anti-inflammatory and anti-oxidant effect
4. Reduction of circulating levels of remnant
5. Stabilizing effect on atherosclerotic plaque
6. Reduction of hepatic production of VLDL
7. Inhibition of hepatic triglyceride synthesis
8. Increased mechanisms of hepatic beta-oxidation
9. Reduction of blood pressure

## Anti-inflammatory and antioxidant metabolic effects

EPA, as well as its purified formulation IPE, has a large number of bioactive and cardioprotective properties including stabilization of membrane lipids, inhibition of lipid oxidation and down-regulation of some genes promoting pathways pro-inflammatories such as NF-κB, PPARα, and TNFα5. In particular, IPE is incorporated into cell membranes and is able to penetrate into atheromatous plaques; here it exerts its local anti-inflammatory properties. Once EPA has been incorporated into cell membranes, their stability is enhanced even in the face of increased cholesterol loads, resulting in a protective effect against endothelial dysfunction. Furthermore, some studies have shown that omega-3 s reduce the differentiation of native T cells into Th1, which represent the main cells found in atheromatous plaques, as well as a proinflammatory marker of adaptive immunity.[7]

Another mechanism by which EPA can confer anti-inflammatory properties is the competition with arachidonic acid for the cyclooxygenase and lipoxygenase enzymes: while the metabolism of arachidonic acid leads to the formation of proinflammatory substances, the metabolism of EPA determines the formation of anti-inflammatory drugs called resolvins, capable of reducing the migration of polymorphonuclear cells, the production of proinflammatory leukotrienes and neutrophil chemotaxis.[9]

IPE therapy has been shown to be associated with the reduction of several serum inflammatory markers such as adiponectin, IL-6, IL-10, and pentraxin-3. In the ANCHOR study population, IPE resulted in a significant improvement in serum values of hsCRP, ox-LDL, and EPA/AA ratio.[10]

## Reduction of remnant lipoproteins

In addition to triglyceride values, great attention has recently been paid to remnant lipoproteins (RLP-C), recognized as highly atherogenic. In fact, these particles contain up to four times the concentration of cholesterol compared to LDL, thus potentially resulting much more atherogenic. Indeed, in the ANCHOR and MARINE studies, IPE therapy was shown to result in a reduction in RLP-C of up to 30% compared to placebo (by−25.8%, $P = 0.0001$ and−29.8%, $P = 0.004$, respectively), being able to partially explain the beneficial effects of this therapy that go beyond the reduction of triglyceride values.

## Stabilizing effect on atheromatous plaque

The EVAPORATE study provides important mechanistic information regarding the therapeutic effect that IPE exerts on the characteristics of vulnerable atheromatous plaques, from growth reduction to the induction of true plaque regression. In particular, it was also observed that the total volumetric progression rates of fibroadipose component plaques were −34% in the IPE group compared to a progression of 32% in the placebo group ($P = 0.0002$). Furthermore, this reduction in plaque volume progression was not accompanied by a significant reduction in LDL cholesterol and triglycerides from baseline10. It is interesting to note how, compared to the data existing in the literature regarding the effects of statins on the volume

of coronary plaques, the data emerging from the EVAPORATE study are surprising, since the effect of IPE would appear to be more effective than an intensive therapy with statins on the stabilization and regression of atheromatous plaque.[11,12]

## Final considerations and current indications for the use of icosapent ethyl

The EMA has approved the use of IPE (marketed under the name of Vazkepa) in Europe in adult patients with established cardiovascular disease or in the presence of diabetes and another cardiovascular risk factor, only if already treated with statins and with a serum triglyceride value ≥150 mg/dL. The dosage is two capsules twice a day.

The IPE has therefore become, to all intents and purposes, an integral part of the therapeutic armamentarium available to clinicians for all those patients in whom a high cardiovascular risk persisted despite the use of the best medical therapies of the moment. Further studies are still needed to fully understand the mechanism of action of the molecule, still partially unknown, and to determine whether other populations of patients at high cardiovascular risk who do not meet the current prescribing criteria can benefit from this therapy.

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## Data availability

No new data were generated or analysed in support of this research.

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