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EDITORIAL

Icosapent ethyl: insights into cardiovascular residual risk

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Atherosclerosis, a multifocal immune-inflammatory disease, represents the leading cause of cardiovascular (CV) morbidity and mortality worldwide.[1] Based on multiple and strong evidence, low density lipoprotein (LDL-c) has always been considered the main target to focus on to achieve atherosclerotic burden reduction.[2-4] Among dyslipidemia players, triglycerides (TGL) have historically been looked at as the neglected factor to further decrease the residual CV risk, until recently.[5]

Evidence regarding the efficacy of TGL lowering therapy has always been murky; although many principles have been tested such as niacin, fibrates, ezetimibe, and omega-3 fatty acids (ω-3 FA), none of them proved to be positively impactful on CV outcome despite TGL levels reduction. The debate about the rationale of a TGL lowering intervention seemed to be definitively closed, until the unsettling positive results of the Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (REDUCE-IT) Trial,[6] which re-opened the way to the study of the topic and induced leading scientific societies to update their recommendations. Bhatt *et al.* randomized 8179 high CV risk patients with raised TGL levels (150-499 mg/dL) on statin therapy (LDL-c 40-100 mg/dL) to icosapent ethyl (IPE) or placebo. High CV risk was defined as mild to moderate TGL elevation and established CV disease (secondary prevention cohort) or diabetes mellitus with at least one risk factor for CV disease and age ≥50. IPE, a novel purified ethyl ester of eicosapentenoic acid, at a dose of 4 g/day reduces TGL by 33.1% by enhancing their clearance from circulating very-LDL particles, reducing VLDL-TGL synthesis and secretion, decreasing lipogenesis and increasing mitochondrial and peroxisomal beta-oxidation of fatty acids. Furthermore, it has many cardioprotective pleiotropic effects: anti-inflammatory and antioxidant, endothelial and membrane stabilizing, antiplatelets and vasodilatory (Figure 1). This landmark trial achieved its prespecified endpoints paving the way to the need of further CV risk reduction even under optimal statin therapy. Specifically, treatment with IPE led to a lower incidence of the composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularization or unstable angina requiring hospitalization (17.2% *versus* 22%, P<0.001) with a relative risk reduction of 25%. The key secondary endpoint was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke. Other endpoints evaluated included individual cardiovascular death, MI, stroke, coronary revascularization, sudden cardiac death, cardiac arrest, and hospitalization for unstable angina. The greatest absolute reduction in ischemic events was experienced by patients with the highest baseline TGL levels, confirming findings from seminal Japan EPA lipid Interven-

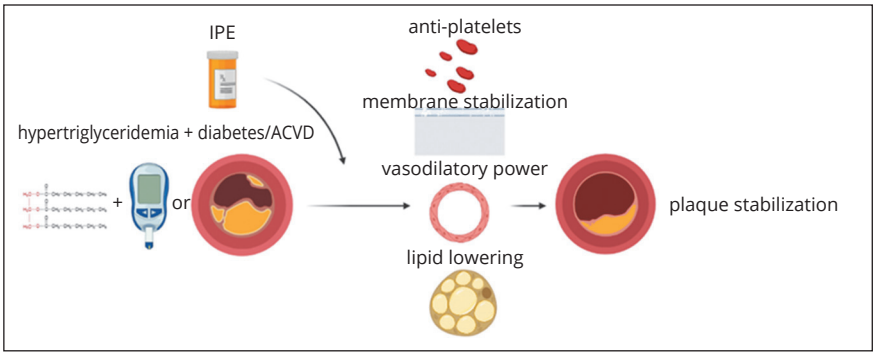

Figure 1.—Cardioprotective pleiotropic effects of icosapent ethyl (IPE). Apart from reducing lipogenesis and triglycerides levels, IPE has many beneficial effects for plaque stabilization: anti-inflammatory and antioxidant effect, endothelial and membrane stabilization, antiplatelets and vasodilatory power.

tion Study (JELIS). Subsequent analyses have strengthened REDUCE-IT results in higher CV risk subgroups, including patients with prior MI, prior coronary revascularization, diabetes and severe renal impairment.

Afterwards, other trials tested higher dose of ω-3 FA formulations (but still less purified formulation), founding out no improvement in clinical outcome, such as the STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia)[7] and OMEMI (Omega-3 fatty acids in Elderly patients with Myocardial Infarction).[8] These results mirrored those from a meta-analysis of 10 trials involving 77,917 individuals on the association of ω-3

TABLE I.—*Key randomized trials on Eicosapentaenoic acid.*[6-10]

Study	Sample size	Inclusion criteria	Intervention	Control	Primary endpoint
REDUCE-IT[6]	8179	Age ≥45 years + established CVD or age ≥50 years + diabetes or additional risk factor + TGL 135-499 mg/dL, LDL-c 41-100 mg/dL on statins	IPE 2 gr twice daily	Placebo	Composite of CV death, non-fatal stroke, non-fatal MI, coronary revascularization, UA
JELIS[6]	18,645	Age 50-75 years or postmenopausal-75 years + total cholesterol ≥6.5 mmol/L (LDL-C 4.4 ≥mmol/L)	EPA ethyl ester 600 mg thrice daily + pravastatin ≥10 mg daily or simvastatin ≥5 mg daily	Pravastatin ≥10 mg daily or simvastatin ≥5 mg daily	Composite of MACE (including: SCD, MI, UA, PCI, CABG, changing in plaque characteristics assessed by IVUS)
STRENGHT[7]	13,078	Age ≥18 years with (or at high risk of) CVD and TGL 180-500 mg/dL, HDL <42 mg/dL (men) or 47 mg/dL (women)	ω-3 CA 4 gr daily	Placebo	Composite of CV death, MI infarction, stroke, coronary revascularization, UA
OMEMI[8]	1027	Age 70 to 82 years with recent (2-8 weeks) MI	1.8 g n-3 PUFA (930 mg eicosapentaenoic acid and 660 mg docosahexaenoic acid)	Corn oil	Composite of non-fatal MI, unscheduled revascularization, stroke, all-cause death, heart failure hospitalization
MARINE[9]	229	Age ≥18 years + TGL 500-2000 mg/dL	IPE 1-2 gr twice daily	Placebo	Median percentage of change in TGL from baseline
ANCHOR[10]	702	Age ≥18 years + high risk for CVD on statins + TGL 200-499 mg/dL, LDL-C 40-99 mg/dL	IPE 1-2 gr twice daily	Placebo	Median percentage of change in TGL from baseline

CVD: cardiovascular disease; TGL: triglycerides, HDL: high density lipoprotein; LDL: low density lipoprotein; IPE: icosapent ethyl; MI: myocardial infarction; MACE: mayor cardiovascular events; SCD: sudden cardiac death; UA: unstable angina; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass grafting.

FA supplementation with CV risk[9] (Table I).[6-10] Some concerns about the positive outcomes seen in the IPE arm has been also attributed to the passive negative effects of the assumption of the 'placebo' mineral oil, accused to be responsible of the increase in the atherogenic cholesterol and inflammatory marker. Even considering the laxative effect (and therefore the possible reduced absorption of statins) of mineral oils, it would still not be sufficient to justify a relative risk reduction of 25% in the IPE group.

At this point it may be legitimate to ask what the explanation behind the outstanding but still counter-current results of REDUCE-IT could be. Certainly, part of the explanation lies in the formulation of IPE, stable and much more purified prodrug compared to previously tested formulations, achieving effective concentration. Another determining influence may be attributable to the plethora of cardioprotective pleiotropic effects described for IPE, such as its plaque stabilizing effects, sufficient to justify the beneficial impact on cardiovascular outcomes. Moreover, the recent effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy (EVAPORATE) Trial proved that treatment with IPE reduces vulnerable atherosclerotic plaque burden defined by coronary computed tomography parameters, a strong predictor of adverse future events.[10] The third explanation could lie in the selected choice of a sample population with high CV risk profile, corresponding to that slice of the population in which clinicians cannot be satisfied by CV risk reduction, but must aim at its elimination.

This last point could be both the solution to our question and the starting point for new insights. In the era of precision medicine and of ever more advanced technologies, ever finer diagnostic tools and ever more elaborate therapeutic protocols, the field of prevention cannot be overlooked. This is especially true in patients at the highest risk of CV events, in which we need to invest all the weapons at our disposal to be incisive on the outcome.

Indeed, based on REDUCE-IT data, main scientific societies indicate IPE in the reduction of residual CV risk in patients on statin treatment with elevated fasting TGL levels and established cardiovascular disease or diabetes with an additional CV risk factor. In this category, the 2021 American College of Cardiology expert consensus[11] (in line with other societies) proposed the use of IPE particularly in high-risk patients with target LDL-c and persistent hypertriglyceridemia despite optimization of dietary (intake of lipids and carbohydrates) and lifestyle control. Beyond current recommendations, having to identify in common clinical practice the patient who could benefit most from this additional therapy, it would probably be the patient with residual 10-year CV risk and frailty due to comorbidities, such as has been outlined in REDUCE-IT, which must be the starting point for designing a patient-tailored therapy.

To draw to a close, the philosophy of "less is more" is often followed in real-life medical world, but in the setting of cardiovascular prevention less is less, and more is mandatory.

Key messages

- Atherosclerosis, a multifocal immune-inflammatory disease, represents the leading cause of cardiovascular (CV) morbidity and mortality worldwide.
- IPE, a novel purified ethyl ester of eicosapentaenoic acid, reduces TGL by 33.1%. Furthermore, it has many cardioprotective pleiotropic effects: anti-inflammatory and antioxidant, endothelial and membrane stabilizing, antiplatelets and vasodilatory.
- According to REDUCE-IT Trial, treatment with IPE led to a lower incidence of the composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularization or unstable angina requiring hospitalization (17.2% *versus* 22%, P<0.001) with a relative risk reduction of 25%.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Antonella Scala, Michela Casella, Chiara Bernelli and Simone Biscaglia contributed equally to the manuscript. All authors read and approved the final version of the manuscript.

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