


Metabolic syndrome cardiovascular risk prevention by omega-3 polyunsaturated fatty acids

Magnus Bäck ^{1,2,3,4,*} and Roberto Latini^{1,5,*}

¹CardiovascularREsolution of INflammation to promote HEALTH (CARE-IN-HEALTH) Consortium; ²Department of Cardiology, Heart and Vascular Center, Karolinska University Hospital, Stockholm, Sweden; ³Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; ⁴Nancy University Hospital, University of Lorraine and INSERM U1116, 9 avenue de la Foret de Haye, BP 20199, 54505 Vandoeuvre les Nancy Cedex, France; and ⁵Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri—IRCCS, Via Mario Negri, 2, 20156 Milano, Italy

Online publish-ahead-of-print 12 November 2023

This editorial refers to ‘Effectiveness of icosapent ethyl on first and total cardiovascular events in patients with metabolic syndrome, but without diabetes: REDUCE-IT MetSyn’, by M. Miller et al. <https://doi.org/10.1093/ehjopen/oead114>.

Studies of cardiovascular (CV) preventive strategies with high-dose omega-3 polyunsaturated fatty acids (n-3 PUFA) in subjects with hypertriglyceridaemia have generated differential results, which may relate to PUFA formulations, dosing and relative content of the two n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).¹ The n-3 PUFA-induced triglyceride lowering has also been suggested to be independent of the either beneficial or neutral cardiovascular outcomes in hypertriglyceridaemic subjects.^{1,2} Importantly, hypertriglyceridaemia is one of the criteria for metabolic syndrome (MetSyn) combined with increased waist circumference and blood pressure as well as high glucose and low HDL levels.

In this issue of *European Heart Journal Open*, a pre-specified MetSyn subgroup analysis, including 35% of the 8179 patients enrolled in REDUCE-IT,³ showed an applicability of the beneficial effects of the EPA formulation icosapent ethyl (IPE) on the primary composite endpoint in subjects with MetSyn without diabetes.³ Among the endpoint components, myocardial infarction, coronary revascularization, and unstable angina requiring hospitalization were significantly lower in IPE vs. placebo in line with results obtained in the total study population.² In contrast, the reduced risk for cardiovascular death and stroke in REDUCE-IT² were not significant in the REDUCE-IT MetSyn subgroup,³ which may illustrate the increased MetSyn risk profile. Finally, IPE increased hospitalization for either atrial fibrillation or flutter events in the MetSyn subgroup and did not alter risk of new onset diabetes.³

The authors conclude that these results support that IPE reduces the high CV risk MetSyn phenotype despite lacking robust effects on MetSyn components apart from triglyceride lowering.³ Interestingly, an analysis of the individual MetSyn components (except triglycerides) revealed that IPE significantly reduced primary endpoint risk

independently of the fulfilment of the waist circumference and elevated fasting glucose MetSyn criteria at baseline.³ In contrast, the IPE-induced effects were less pronounced and non-significant in the absence of blood pressure and HDL criteria.³

One of the challenges in the interpretation of variable results of cardiovascular outcomes in clinical trials of omega-3 PUFA in addition to differences in doses, formulations and the EPA/DHA content, is identifying factors distinguishing responders from non-responders to omega-3 PUFA treatment.¹ Differential effects of IPE depending on the MetSyn criteria³ opens up for future studies of blood pressure and HDL as possible factors to take into consideration in a personalized dimension for n-3 PUFA indications in cardiovascular prevention. Other possible underlying factors to a personalized response to n-3 PUFA intake and supplementation include genetic variations in fatty acid metabolism. For example, polymorphisms within the fatty acid desaturases (FADS) 1 and 2 FADS loci alter desaturase activity, which influence PUFA levels following n-3 PUFA supplementation or dietary intake and associate with measures of cardiovascular risk.⁴

Omega-3 PUFAs also serve as the substrate for bioactive lipid mediators. The release of EPA from IPE provides the precursors for biosynthesis of resolvins E1, which mediates an active resolution of inflammation.¹ The contribution of low-grade non-resolving chronic inflammation in atherosclerotic cardiovascular disease has been well established. MetSyn represents an increased inflammatory state and median plasma concentration of hsCRP were slightly elevated (1.9 mg/L) in the REDUCE-IT MetSyn population.³ Previous reports on biomarkers in REDUCE-IT indicated minor changes in hsCRP levels by IPE treatment.⁵ No prospective data were provided for the effects of treatment on hsCRP in subjects with MetSyn, and potential changes in the MetSyn components measures were also not reported in the REDUCE-IT MetSyn subgroup analysis.³

The results presented in this issue of *European Heart Journal Open* that IPE reduced cardiovascular events in subjects with MetSyn³ extends the knowledge on omega-3 PUFA in cardiovascular prevention. The observations on IPE cardiovascular risk prevention according to MetSyn criteria add new clues to the genetic and

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal Open* or of the European Society of Cardiology.

* Corresponding author. Tel: +46 8 12380000, Email: Magnus.Back@ki.se (M.B.); Email: roberto.latini@marionegri.it (R.L.)

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

inflammation paths that are currently followed in the quest for identifying responders and non-responders to omega-3 PUFA cardiovascular prevention.

Data availability

No new data were generated or analysed in the preparation of this editorial.

Disclosure

Magnus Bäcks' institution has received speaker and consultant fees from Amarin, Amgen, Heel, Novartis, and KabiFresenius.

Funding

CARE-IN-HEALTH is funded by the European Union within HORIZON EUROPE Health Framework Programme under grant agreement 101095413. Views and opinions expressed are however those of the authors and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency.

Conflict of interest: None declared.

References

1. Bäck M. Icosapent ethyl in cardiovascular prevention: resolution of inflammation through the eicosapentaenoic acid—resolvin E1—ChemR23 axis. *Pharmacol Ther* 2023;**247**: 108439.
2. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;**380**:11–22.
3. Miller M, Bhatt DL, Brinton EA, Jacobson TA, Gabriel Steg Ph., Pineda AL, Ketchum SB, Doyle RT Jr, Tardif J-C, Ballantyne CM; on Behalf of the REDUCE-IT Investigators. Effectiveness of icosapent ethyl on first and total cardiovascular events in patients with metabolic syndrome, but without diabetes: REDUCE-IT MetSyn. *Eur Heart J Open* 2023;doi:10.1093/ehjopen/oead114.
4. Bäck M, Xhaard C, Rouget R, Thuillier Q, Plunde O, Larsson SC, Girerd N, Ferreira JP, Boivin JM, Bozec E, Merckle L, Zannad F, Hoge A, Guillaume M, Dandine-Roulland C, Floch EL, Bacq-Daian D, Deleuze JF, Van den Berghe L, Nazare JA, Laville M, Branlant C, Behm-Ansmant I, Wagner S, Rossignol P. Fatty acid desaturase genetic variations and dietary omega-3 fatty acid intake associate with arterial stiffness. *Eur Heart J Open* 2022;**2**:oeac016.
5. Ridker PM, Rifai N, MacFadyen J, Glynn RJ, Jiao L, Steg PG, Miller M, Brinton EA, Jacobson TA, Tardif JC, Ballantyne CM, Mason RP, Bhatt DL. Effects of randomized treatment with icosapent ethyl and a mineral oil comparator on interleukin-1beta, interleukin-6, C-reactive protein, oxidized low-density lipoprotein cholesterol, homocysteine, lipoprotein(a), and lipoprotein-associated phospholipase A2: a REDUCE-IT Biomarker Substudy. *Circulation* 2022;**146**:372–379.