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The reduction in cardiovascular risk in REDUCE-IT is due to eicosapentaenoic acid in icosapent ethyl

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This commentary refers to 'A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs', by T. Doi *et al.*, https://doi.org/10.1093/eurheartj/ehab555 and the discussion piece 'Mineral oil and icosapent ethyl may jointly explain the between arm difference of cardiovascular risk in REDUCE-IT' by T. Doi *et al.*, https://doi.org/10.1093/eurheartj/ehab764.

We have read with interest the analysis trying to emulate the results of the REDUCE IT and STRENGTH trials using the Copenhagen observational database.[1] We wish to share several concerns with the authors regarding their assumptions. The analysis assumes that lipid profile differences account for treatment and placebo effects when there are potential myriad other intermediate/surrogate markers. It examined relatively small differences in certain biomarkers, but did not factor in the very large change in eicosapentaenoic acid (EPA) levels that occurred in REDUCE-IT. The latter likely explains the bulk of benefit seen in that trial due to downstream effects of EPA that basic scientists are still unravelling.[2] Our main concern is that such an analysis attempting to correlate clinical benefits of EPA to changes in selected surrogate biomarkers can miss major causal known or unknown pathways. The recent demonstration of major cardiovascular benefits of SGLT2 inhibitors despite a moderate glucose-lowering effect exemplifies the potential disconnect between selected surrogate biomarkers and outcomes.

In addition, the authors regrettably did not have access to changes in lipid and high sensitivity C-reactive protein (hs-CRP) profiles during follow-up in their study, so instead they compared differences in baseline lipid and hs-CRP profiles and correlated them to differences in risk. Unfortunately, this is problematic because there are major confounding differences between patients compared on the basis of their baseline characteristics (in contrast to what happens in a randomized trial where all things are equal at randomization). In addition, the effect of differences in biomarkers on risk is exaggerated because differences in baseline risk reflect lifetime exposure to different levels of LDL, apo B, triglycerides, and hs-CRP up to enrolment, as opposed to short-term changes, as would be seen in a prospective trial.

The issue of placebo choice and changes in biomarkers has been thoroughly reviewed by the US FDA, Health Canada, and the European Medicines Agency, who all concluded that any theoretical effect of placebo choice on the 25% risk reduction seen in REDUCE-IT would have been very small.[3] In addition, icosapent ethyl has also been studied in two other randomized trials which did not use any placebo and still showed clear benefit—JELIS with a significant 19% reduction in clinical endpoints and CHERRY with a significant benefit on intravascular ultrasound endpoints.[4,5] While clinical events are far more important than any biomarker changes, for those who are concerned about such issues, data from PREPARE-IT 1 will provide another opportunity to assess any effects of pharmaceutical grade mineral oil placebo on hs-CRP levels, including with use of a higher loading dose of placebo in that trial.

The totality of evidence of randomized clinical trials (with and without use of a placebo), imaging data, observational data, and basic science data all support an important biological and clinical effect of EPA. As the authors themselves state,[1] the available data 'support the European guideline recommendations to consider use of omega-3 fatty acids (icosapent ethyl 2 × 2 g/day) in combination with a statin in high-risk patients with triglyceride levels between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment'.

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