Were the drug and patient population studied in the REDUCE-IT® trial the same as that in the STRENGTH trial?

The drug, dose of EPA and patient population studied in REDUCE-IT® were different from that evaluated in STRENGTH.

REDUCE-IT evaluated VASCEPA® (icosapent ethyl or IPE), which is an innovative and stable form of eicosapentaenoic acid (EPA). STRENGTH studied EPANOVA® (omega-3 carboxylic acids), which is an omega-3 fatty acid mixture containing DHA and various other ingredients.

There are biological differences between these ingredients, including important differences between EPA and DHA. *In vitro*, *in vivo,* and clinical studies have reported numerous differences in the biological effects of EPA and DHA. For example, EPA has different tissue distribution, different transcriptional, antioxidant, and membrane-stabilizing effects than DHA or omega-3 fatty acid mixtures containing DHA. The anti-inflammatory mechanisms of action may be different for EPA than for DHA as presented by Stephen Nicholls, MD at the American College of Cardiology medical congress and published in the *European Medical Journal* as a recap and in the *Journal of the American College of Cardiology* as an abstract.[1,2]

The dose of EPA in the two studies was also different, with the REDUCE-IT study dosed at 4g/day of EPA and the STRENGTH study dose at 4g/day of an omega-3 mixture which included EPA, DHA and other ingredients. The STRENGTH study dosing included the delivery of at least 850 mg of polyunsaturated fatty acid (PUFA) per capsule, including approximately 550 mg EPA, 200 mg DHA and 100 mg other PUFA, all of which may be potentially pharmacologically active in differing ways and to varying degrees. With different drugs and in different chemical forms (i.e., ethyl esters vs. carboxylic acid), different clinical effects were expected. Historically, cardiovascular outcomes studies of omega-3 mixtures which include DHA have consistently failed to demonstrate cardiovascular benefit.

The patient populations studied in REDUCE-IT and STRENGTH also differed. In REDUCE-IT, patients had statin stabilized LDL-C of >40 to ≤100 mg/dL, but had persistently elevated triglyceride levels of ≥135 to <500 mg/dl, and were either ≥45 years of age with established cardiovascular disease (71% of enrolled patients) or ≥50 years of age with diabetes with more than one additional risk factor (29% of enrolled patients).

In the STRENGTH study, patients had statin-stabilized LDL-C of <100 mg/dL, triglyceride levels of ≥180 to <500 mg/dL, and HDL-C of <42 mg/dL for men or HDL-C of <47 mg/dL for women. The patients were ≥18 years of age and at high risk for a future cardiovascular event with at least one of the following criteria: any atherosclerotic cardiovascular disease; history of diabetes mellitus (type 1 or 2); patients who were ≥40 years of age for men and ≥50 years of age for women, plus one of the risk factors; or patients who were >50 years of age for men or >60 years of age for women, with at least one of the risk factors defined in the protocol. Final enrollment included 56% of patients with established cardiovascular disease.

There is scientific value in all clinical trials. From REDUCE-IT and STRENGTH we learned the cardiovascular outcomes results of two different drugs. For the two drugs that were studied, one demonstrated clinical benefit and one did not. There is value in this knowledge. The fact that there was no clear evidence of cardiovascular benefit in STRENGTH, whereas other studies of omega-3 mixtures included some non-significant trends towards benefit, suggest each chemical form of a drug has a different clinical effect and

should be studied separately. These results suggest, similar to various diabetes drugs, that not just the drug which is delivered matters but also how it is delivered. Furthermore, it is not possible to predict the results of such cardiovascular outcomes studies based on changes in lipid markers, such as triglyceride levels. The only way to predict clinical results are through robustly conducted clinical study.

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[1] Pisaniello AD, Nicholls SJ, Ballantyne CM, Bhatt DL, Wong ND. Eicosapentaenoic acid: atheroprotective properties and the reduction of atherosclerotic cardiovascular disease events. *EMJ*. 2020;5:29-36.

[2] Di Bartolo BA, Liu G, King PM, Gibson RA, Tan JTM, Nicholls SJ. Eicosapentaenoic acid ameliorates vascular inflammation: a mechanistic rationale for its atheroprotective effects [abstract]. *J Am Coll Cardiol* 2020;75(11 suppl 1):3661.