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# Resolving Reduce-It: A Proposal for the “Resolve-It” Study

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**Opinion**

Two recent trials of the use of fish oils in the treatment of hyperlipidemia have demonstrated totally different results. REDUCE-IT demonstrated a 25% reduction in a 5- point MACE (major adverse cardiovascular events) comprised of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina using a purified form of ethyl eicosapentaenoic acid (EPA) at a dose of 4 grams/day [1]. Another similarly designed trial, STRENGTH [2], using a 4g carboxylic acid formulation of EPA and docosahexaenoic acid (DHA) was stopped early due to futility. The principal question raised by the striking difference in outcomes of these two trials concerns the use of a mineral oil placebo in REDUCE-IT and whether it may have functioned as an inflammatory stimulus unlike the corn oil placebo of STRENGTH [3]. Subjects randomized to mineral oil had a 4.2% increase in LDL-C, a 38.5% increase hs CRP, and an increase in several biomarkers of inflammatory risk after 2 years' treatment (4) As a result there have been calls for another outcomes study that is designed to address this controversy [4]. To address the above question it is proposed, based on a previous small study of EPA used in the treatment of acute myocardial infarction (MI) [5], a second similar but larger study be performed. The initial study by Doi et al was a prospective, open-label, blinded endpoint, randomized trial that consisted of 115 patients with acute MI. They were randomly assigned to the EPA group (57 patients) and the control group (58 patients) added to a statin background. After percutaneous coronary intervention (PCI), 1800 mg/day of EPA was initiated within 24 h. The primary endpoint was composite events, including cardiac death, stroke, re-infarction, ventricular arrhythmias, and paroxysmal atrial fibrillation within 1 month.

They demonstrated that early EPA treatment after PCI in the acute stage of MI reduces the incidence of ventricular arrhythmias and lowers CRP values.

For the larger “RESOLVE-IT” study it is proposed that patients would be double blinded and randomized into one of two groups following percutaneous coronary intervention (PCI) for the treatment of acute myocardial infarction. In one group treatment would consist of 2 g twice daily of ethyl EPA + 2 g of the mineral oil placebo of the REDUCE-IT study. And the second group would receive 2 g twice daily of ethyl EPA + capsules containing water matching the size and appearance of mineral oil capsules. As in the study by Doi, all patients would be on a background of moderate to high intensity statins plus other interventions considered part of routine care for MI patients undergoing PCI. And all patients would receive active treatment with ethyl EPA.

The study would be powered for the same 5 point MACE studied in REDUCE-IT plus new onset atrial fibrillation. CRP and other markers would be obtained, both for inflammation and endothelial function, as well as lipid parameters. That this study would be done in acute MI which involves higher risk patients than the 4000+ studied in REDUCE-IT or STRENGTH would mean that the number needed would be less. If the two groups perform equally, the placebo would not be an issue for the results of REDUCE-IT. The mineral oil placebo had no effect and the results of REDUCE-IT need no reconsideration. If, however, a difference is seen the study would be subject to early termination by the data safety monitoring board. A difference, especially if seen early, may resolve the question of mechanism of benefit, lowering triglyceride

levels or improving endothelial function with an anti-inflammatory effect [6,7], seen from EPA. If, as previously suggested [3], the group receiving mineral oil is found significantly do better than the group receiving water capsules the results of REDUCE-IT will have to be revised downward. Mineral oil would be the equivalent of a drug [3] and the reduction in overall risk from triglyceride lowering by EPA would be exaggerated by the mineral oil placebo.

Finally, if the group receiving water capsules performs better, one could consider mineral oil with its effect of increasing hsCRP as having masked the action of EPA on endothelial function. That is, EPA's benefit on reducing events is related to improving endothelial function [6,7], with its anti-inflammatory effects, and not triglyceride lowering, a finding that would be relevant in view of the recently negative PROMINENT study [8]. Concerning the use of a water placebo instead of the corn oil placebo used in STRENGTH [3], this concerns the negative result seen in STRENGTH despite triglyceride lowering comparable to that seen in REDUCE-IT [2]. Although unlikely that the corn oil placebo used in STRENGTH was in any way responsible for the negative outcome of that study, this possibility has never been excluded. Using a water placebo removes any possibility of an effect of a corn oil placebo in the above proposed study.

To conclude, the controversy surrounding the placebo used in REDUCE-IT continues along with the need for a better understanding of the mechanisms involved in any reduction of risk by ethyl EPA. The study currently being proposed may "RESOLVE-IT".

### Acknowledgement

None.

### Conflict of Interest

No conflict of interest.

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