Letter by Halcox Regarding Article, "OMEGA, A Randomized, Placebo-Controlled Trial to Test the Effect of Highly Purified Omega-3 Fatty Acids on Top of Modern Guideline-Adjusted Therapy After Myocardial Infarction"

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Circulation. 2011;124:e21
doi: 10.1161/CIRCULATIONAHA.110.016287
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Correspondence

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To the Editor:

I read with interest the results of the OMEGA trial,[1] in which the addition of omega-3 polyunsaturated fatty acid (PUFA) ethyl esters to modern, evidence-based treatment of patients who had had a recent myocardial infarction (MI) did not significantly reduce the primary end point of sudden cardiac death (SCD) or other clinical events within 1 year. As would be expected in a trial of contemporary therapy, 78% of OMEGA trial patients underwent coronary revascularization, and 94% received a statin on discharge, in contrast to 5% who underwent coronary revascularization and 29% who received lipid-lowering drugs even after 6 months in the earlier GISSI-P trial.[2] An appropriately designed trial of omega-3 PUFAs in the context of modern management of post-MI patients is therefore highly desirable.

The absence of significant benefits from omega-3 PUFAs might be explained in part by the OMEGA study design. Sample size was calculated by the use of available MI registry and clinical trial data, the anticipated risk profile of the patients to be enrolled, and with the expectation of a 45% reduction after 1 year in the relative risk of SCD with omega-3 PUFA treatment as seen in GISSI-P. Thus, 1-year SCD rates of 3.5% in the control group and 1.9% in the treated group were predicted. It is significant that the SCD rate in the OMEGA study cohort was >50% lower than anticipated: 1.5% at 1 year in both the placebo and treatment groups. This presumably resulted from modern treatment practices and, as acknowledged, the possible contribution of the lower than anticipated risk profile of the trial population. Consequently, OMEGA was underpowered for the primary end point. Considering the ongoing improvements in acute treatment and secondary prevention since the GISSI-P trial, it may have been reasonable to assume lower rates for overall mortality, the proportion of deaths resulting from SCD, or the relative risk reduction for SCD achieved with active therapy. Although the investigators stated it was not feasible to adopt an event-driven protocol or to enroll the number of patients (≈20 000 rather than 4000) necessary to achieve statistical power with the lower event rates observed, it should be acknowledged that firm conclusions cannot be drawn from this underpowered study.

In addition, the 1-year duration of the OMEGA trial aimed to investigate the early benefits of omega-3 PUFAs shown by a post hoc time-course analysis of the first year of treatment in the GISSI-P trial.[3] However, more recent trials, such as the GISSI-HF[4] and JELIS[5] trials, have shown ongoing benefits of omega-3 PUFAs when taken for >3 years. Thus, a longer follow-up period could have increased the power of the OMEGA trial and may also have revealed longer-term benefits of highly purified omega-3 PUFAs post-MI.

In light of these important limitations and the consequent difficulty in drawing confident conclusions, changes to current practice in the use of highly purified omega-3 PUFAs for post-MI patients cannot be justified on the basis of the OMEGA trial data. Adequately powered studies are mandatory to elucidate the efficacy and tolerability of high-dose omega-3 PUFAs when given alongside modern evidence-based therapies post-MI.

Acknowledgments

Medical writing support was provided by Gail Rickard.

Sources of Funding

This work was funded by Abbott Laboratories.

Disclosures

Dr Halcox has received honoraria for lecturing and consultancy fees from Abbott Laboratories.

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(*Circulation*. 2011;124:e21.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.016287**