Low Doses of n-3 Fatty Acids Do Not Reduce Major Cardiovascular Events

Investigators in the ALPHA OMEGA Trial (NCT00127452) concluded that that low doses of n-3 fatty acids, given in the form of enriched margarines, do not reduce major cardiovascular (CV) events. The results of the trial were presented by Daan Kromhout, MD, Wageningen University, Wageningen, The Netherlands, and were in accordance with those of prior studies by Saravanan and colleagues [Saravanan P et al. *Lancet* 2010]. They concluded that the effect of n-3 fatty acids diminished with increasing drug treatment of CV risk factors and that no effect was observed in state-of-the-art-treated patients in the most recent trial.

The ALPHA OMEGA Trial was designed to examine the effects of low doses of the n-3 fatty acids eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and/or ALA in margarine (targeted average intake = 20 g/day) in stable Dutch post-MI (≤10 years) patients (n=4837; 78% men). Subjects (mean age 69 years; range 60 to 80 years) were randomly assigned to receive: EPA-DHA placebo+ALA placebo (n=1236), 400 mg EPA-DHA+ALA placebo (n=1192), EPA-DHA placebo+2 g ALA (n=1197), or 400 mg EPA-DHA+2 g ALA (n=1212) and were followed for 40 months.

The primary study outcome was major CV events. Important secondary endpoints were fatal coronary heart disease and ventricular arrhythmia-related events, defined as sudden death, cardiac arrest, and cardioverter-defibrillator placement.

A total of 671 patients developed a major CV event. There was no difference in either the primary or secondary outcomes between subjects who received EPA+DHA or ALA compared with those who received placebo (Figures 1 & 2). Among subgroups, however, there was a nonsignificant (HR, 0.73; 95% CI, 0.51 to 1.03; p=0.07) 27% reduction in the primary endpoint among women who received ALA. In an exploratory analysis, diabetic subjects (n=1014) who received EPA+DHA showed a 49% (HR, 0.51; 95% CI, 0.27 to 0.97) reduction in coronary heart disease mortality and ventricular arrhythmia-related events (HR, 0.51; 95% CI, 0.24 to 1.11). Subjects who received ALA had a 61% reduction in ventricular arrhythmia-related events (HR, 0.39; 95% CI, 0.17 to 0.88). Adverse events did not differ among the study groups.

Figure 1. EPA+DHA Endpoints.

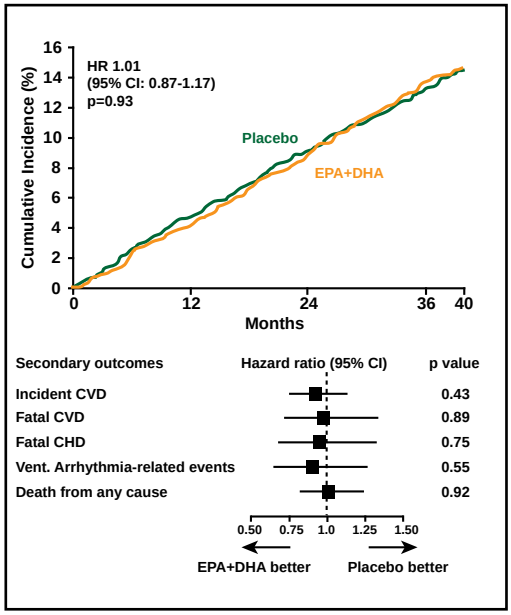

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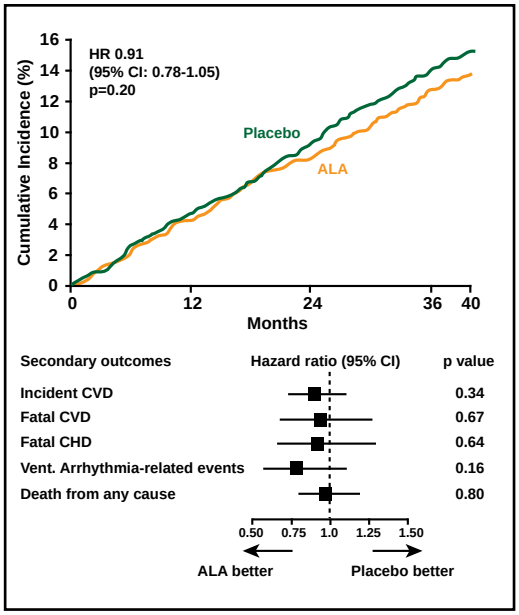
Figure 2. ALA Endpoints.



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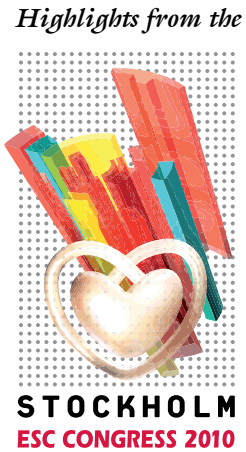

Commenting on the differences between the ALPHA OMEGA Trial and earlier trials, Luigi Tavazzi, MD, Villa Maria Cecilia Hospital, Cotignola, Italy, noted three factors that may have influenced the results: the relatively small sample size, the low dose of EPA-DHA, and whether the components of the composite primary endpoint were specific enough for the specific mechanisms of action of n-3 fatty acids. Of note, the endpoints in question were based on previous prospective cohort studies that demonstrated that n-3 fatty acids lowered the risk of coronary heart disease as well as stroke. While praising the investigators for attempting the trial, Prof. Tavazzi pointed out that clinicians should use caution when using the ALPHA OMEGA Trial results to draw conclusions about the effect of n-3 fatty acids in this studied population.

Results of the ALPHA OMEGA Trial were published online in *the New England Journal of Medicine* at NEJM.org (10.1056/NEJMoa1003603).

Stem Cell Transplantation Improves Heart Function and Survival in Chronic Heart Failure

Injecting autologous stem cells directly into the hearts of patients with heart failure improves hemodynamic function, quality of life, and survival, according to new results from the STAR Heart study. The open-label, nonrandomized study is the largest trial to date that has compared stem cell transplantation with standard therapy for patients with chronic heart failure due to ischemic heart disease.

The STAR Heart study included 391 patients with chronic heart failure, defined as a left ventricular ejection fraction (LVEF) ≤35%. All patients experienced myocardial infarction (MI) that was treated by percutaneous coronary intervention (PCI) for a mean of 8.5 years prior to study enrollment. A total of 191 patients agreed to undergo treatment with autologous stem cell transplantation, and the remaining 200 patients acted as controls. All patients were also receiving optimal medical therapy for heart failure.

The transplant procedure involved harvesting autologous stem cells from the bone marrow and delivering these cells (mean, 66 million) directly into the area of ischemic damage via intracoronary balloon catheter. Patients were examined at 3 months, 12 months, and 5 years after transplantation. Dr. Bodo-Eckehard Strauer, Heinrich-Heine-University of Duesseldorf, Duesseldorf, Germany, reported long-term results from the study.

Within 3 months, patients in the transplant group showed improvements in LV performance compared with baseline, including a 22% improvement in cardiac index ($p<0.01$), 15.4% increase in exercise capacity ($p<0.01$), 11% increase in peak oxygen update ($p<0.05$), and 6.3% increase in oxygen pulse ($p<0.05$). LVEF also increased by 22.4%, from 29.4% at baseline to 36% at 3 months ($p<0.01$). By comparison, all hemodynamic parameters worsened in the control group, including a 0.5% absolute reduction in LVEF ($p<0.05$).

Patients in the transplant group sustained significant improvements in all measures of hemodynamics, exercise capacity, LV contractility, and LV geometry through the 5-year follow-up period. This included a 25.1% increase in LVEF ($p<0.01$), a 4.9% reduction in end diastolic volume ($p<0.5$), a 13.7% reduction in end systolic volume ($p<0.01$), and a 15.1% increase in shortening velocity ($p<0.01$). Patients in the control group showed a significant deterioration in each of these measures from baseline to 5 years ($p<0.05$ for all) despite optimal medical therapy.

Improvements in LV performance were associated with prolonged survival among stem cell recipients. At 5 years, 184 of 191 patients were alive in the transplant group, compared with 168 of 199 control patients ($p<0.01$). Overall, these findings suggest a promising role for autologous stem cell transplantation in improving cardiac function and survival among patients with ischemic cardiomyopathy.

Ivabradine Added to Standard Therapy Improves Outcomes In Patients With Systolic HF

In patients with chronic heart failure (HF), elevated resting heart rate (HR) is a risk factor for adverse outcomes [Fosbøl EL et al. *Int J Cardiol* 2010]. Results of the Systolic Heart Failure Treatment with the *If* Inhibitor Ivabradine Trial (SHIFT; ISRCTN70429960), presented by Michel Komajda, MD, La Pitié-Salpétrière Hospital, Paris, France, indicate that when added to standard therapy, ivabradine reduced HR (Figure 1) and improved outcomes in subjects with systolic HF as early as 3 months [Swedberg K et al. *Lancet* 2010].

All subjects had NYHA class II to IV HF, left ventricular ejection fraction ≤35%, and resting HR ≥70 beats per minute (bpm); received recommended HF therapy (~90% on β-blockers; 56% at target daily dose); and had been hospitalized for worsening HF within the previous 12 months. Participants were randomly assigned to receive either ivabradine (n=3241; 5 mg bid, titrated to a maximum of 7.5 mg based on HR and tolerability) or placebo (n=3264). The primary outcome measure