Omega-3 Fatty Acids, but Not Statin Therapy, Cuts Mortality and Hospitalizations in Heart Failure

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September 3, 2008 — Omega-3 fatty-acid supplementation improves morbidity and mortality in symptomatic heart-failure patients, while statins failed to have any beneficial effect in the same group of patients, two new studies have shown [1,2]. The long-term administration of omega-3 fatty acids reduced all-cause mortality and admission to the hospital for cardiovascular (CV) reasons, while there was no effect on these end points with 10-mg rosuvastatin (Crestor, AstraZeneca).

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) trial — which includes two nested studies designed to test the two hypotheses — was presented here at the European Society of Cardiology (ESC) 2008 Congress and published online in The Lancet.

Speaking to the 9% reduction in all-cause mortality with omega-3 fatty acids in The Lancet, the GISSI-HF investigators write: "Although this moderate benefit was smaller than was expected, we should note that it was obtained in a population already treated with recommended therapies, was consistent across all the predefined subgroups, and was further supported by the findings of the per-protocol analysis."

Chair of the GISSI-HF steering committee, Dr Luigi Tavazzi (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy), who presented the omega-3 fatty-acid data to the media during an ESC press conference, said the treatment is an "effective, safe, simple, and cheap" option for patients with chronic heart failure. In an editorial accompanying the published studies [3], Dr Gregg Fonarow (University of California, Los Angeles) echoed the sentiment, writing that while "questions remain about the mechanism of action, optimum dosing, and formulation, supplementation with n-3 polyunsaturated fatty acids [PUFA] should join the short list of evidence-based life-prolonging therapies for heart failure."

GISSI-HF, polyunsaturated fatty acids, and statins

The GISSI-HF project is a large-scale, randomized, double-blind study designed to investigate the effects of omega-3 fatty acids and statin therapy on mortality and morbidity in patients with symptomatic heart failure. In the PUFA study, investigators enrolled patients with chronic heart failure — NYHA class 2 - 4 regardless of cause and left ventricular ejection fraction — and randomized them to treatment with n-3 PUFA 1 g daily or placebo. Patients were followed for nearly four years, with the co-primary end points being death and death or admission to the hospital for cardiovascular reasons.

After 3.9 years of follow-up, treatment with the omega-3 fatty acids reduced the risk of mortality by 9% and mortality and admission to the hospital for cardiovascular causes by 8%. The absolute reduction in risk was small, just 1.8%, but investigators report that 56 patients would need to be treated to avoid one death and 44 patients would need to be treated to avoid one death or admission for cardiovascular reasons. A per-protocol analysis that included only patients who remained on treatment for the study duration confirmed the overall findings, showing that treatment cut the absolute risk by 3.3% compared with placebo, or a 14% relative risk reduction.

GISSI-HF omega-3 fatty acid study: Primary and secondary outcomes

End point	Omega-3 fatty acids, n=3494 (%)	Placebo, n=3481 (%)	Adjusted hazard ratio (95% CI)
Primary end points			
Mortality	27.3	29.1	0.91 (0.833-0.998)
All-cause mortality or hospitalization for cardiovascular causes	56.7	59.0	0.92 (0.849-0.999)
Secondary end points			
Death from cardiovascular causes	20.4	22.0	0.90 (0.81-0.99)
Sudden cardiac death	8.8	9.3	0.93 (0.79-1.08)
Patients admitted for cardiovascular causes	46.8	48.5	0.93 (0.87-0.99)
Patients with fatal and nonfatal MI	3.1	3.7	0.82 (0.63-1.06)
Patients with fatal and nonfatal stroke	3.5	3.0	1.16 (0.91-1.53)

Speaking to the media, Tavazzi said the advantage of n-3 PUFA, as documented by the primary end points, is that they appear to have a beneficial effect on the mechanisms leading to the progression of heart failure. Although the exact reasons are unknown, omega-3 fatty acids could possibly exert favorable effects on inflammatory processes, such as reductions in endothelial activation and cytokine production, as well as influence platelet aggregation, blood pressure, heart rate, ventricular function, and autonomic tone.

Asked about the differences in outcomes in the GISSI Prevenzione trial, a study where there was a favorable effect of omega-3 fatty acids in patients with myocardial infarction (MI), with n-3 PUFA supplementation reducing the risk of mortality 21%, Tavazzi told heartwire that fatty acids mainly influenced the risk of sudden death in the post-MI patients. In GISSI-HF, on the other hand, the risk of sudden death was not significantly different between the treated and untreated patients, suggesting the "mechanisms of action in heart-failure patients are broader than post-MI patients."

Dr Michel Komajda (Université Pierre et Marie Curie, Paris, France), who commented on the study during the late-breaking clinical trials sessions, said there "is still a bit of

a mystery" regarding the observed benefit, especially as it relates to the mechanism of action. Moreover, the study included few patients with preserved ejection fractions, so further study will be needed to determine whether the benefit extends to them as well.

GISSI-HF and statin therapy

Cochair of the GISSI-HF steering committee, Dr Gianni Tognoni (Istituto di Ricerche Farmacologiche Mario Negri, Milan), presented the data on chronic heart-failure patients treated with rosuvastatin 10 mg. Patients were also followed for nearly four years, with the co-primary end points also being time to death and time to death or admission to the hospital for cardiovascular reasons.

After 3.9 years, there was no significant difference between arms in either of the two co-primary end points. The findings were consistent across all secondary end points as well as consistent across every subgroup analyzed, including older patients, those with left ventricular ejection >40%, and those with and without diabetes. Treatment with rosuvastatin decreased low-density lipoprotein (LDL) cholesterol 27% at three years—down from 123 mg/dL at baseline to 90 mg/dL—and an exploratory analysis revealed no treatment effect based on achieved LDL-cholesterol reductions.

GISSI-HF statin study: Primary outcomes

End point	Rosuvastatin 10 mg, n=2285 (%)	Placebo, n=2289 (%)	Adjusted hazard ratio (95% CI)
Mortality	29.0	28.0	1.00 (0.898-1.122)
All-cause mortality or hospitalization for cardiovascular causes	57.0	56.0	1.01 (0.908-1.112)

Speaking to the media, Tognoni said that the prescription of rosuvastatin or any statin to patients with heart failure should not be considered because the use of the cholesterol-lowering drugs does not translate into any clinically meaningful benefit for heart-failure patients. In his editorial, Fonarow comments that the findings from GISSI-HF, alongside the Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA), "establish that, although statin therapy lowers concentrations of LDL cholesterol, is well tolerated, and seems reasonably safe, it does not produce meaningful improvements in survival in patients with chronic heart failure."

Govern by science, not strongly held opinion

In CORONA, presented and published in November 2007, treatment with rosuvastatin had no significant effect on cardiovascular outcomes, as measured by the primary-end-point composite of CV death, nonfatal MI, or stroke. It did, however, significantly reduce the number of hospitalizations from CV causes and from heart failure. Commenting on the findings during the late-breaking clinical-trials session, Dr Philip

Poole-Wilson (Imperial College London, UK) said GISSI-HF is an important study in light of the CORONA findings.

"What this study has done is extend what we knew from CORONA, a study where more patients had severe heart failure, to those with less severe heart failure," he said. "To that extent, the two trials are really complementary."

Poole-Wilson said that GISSI-HF is likely to generate disappointment among clinicians, as the results of the study, in light of observational and meta-analyses data, were expected to be positive. When the trial was designed, some even expressed concern that it was unethical to randomize heart-failure patients to placebo because they were so confident of the benefit of statin therapy in this patient population. The results, he said, ultimately should humble researchers, especially as they serve as reminder that medical decisions should be guided "science, and not strongly held opinion."

In terms of why the study failed to show a beneficial effect on clinical outcomes, the GISSI-HF investigators note that treatment with rosuvastatin reduced LDL cholesterol as well as high-sensitivity C-reactive protein (CRP) levels. "These effects might no longer affect the progression of coronary artery disease in patients with ischemic heart failure, perhaps because their effect is attenuated by a biological milieu not favoring the progression of coronary artery disease," they write in The Lancet. In his editorial, Fonarow states that once heart failure is established, statins may not allow patients to escape the underlying heart-disease process.

The GISSI studies are a collaboration of the Mario Negri Institute and the Associazione Nazionale dei Medici Cardiologi Ospedalieri. The GISSI-HF studies are sponsored by the Societa Prodotti Antibiotici, Pfizer, Sigma Tau, and AstraZeneca.

Sources

1. GISSI-HF investigators. **Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial.** *Lancet* 2008; DOI: 10.1016/S0140-6736(08)61241-6. Available at: http://www.thelancet.com.

2. GISSI-HF investigators. **Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial**. *Lancet* 2008; DOI: 10.1016/S0140-6736(08)61241-6. Available at: http://www.thelancet.com.

3. Fonarow GC. **Statins and n-3 fatty acid supplementation in heart failure**. *Lancet* 2008; DOI: 10.1016/S0140-6736(08)61239-8. Available at: http://www.thelancet.com.

European Society of Cardiology 2008 Congress. Presented August 31, 2008.

Study Highlights:

- The GISSI-HF was a randomized, double-blind, placebo-controlled trial conducted at 326 cardiology and 31 internal medicine centers in Italy.

- The goal of GISSI-HF was to assess whether omega-3 PUFA could improve morbidity and mortality in a large population of patients with symptomatic heart failure of any cause.

- Enrollment criteria were chronic heart failure of New York Heart Association class II to IV, irrespective of cause and left ventricular ejection fraction.

- A concealed, computerized telephone randomization system was used to randomly assign participants to receive omega-3 PUFA 1 g (n = 3494) or placebo (n = 3481) daily.

- Median follow-up was 3.9 years (interquartile range 3.0 - 4.5).

- Main outcome measures were time to death and time to death or to hospitalization for CV cause.

- Analysis was by intent-to-treat.

- Death from any cause occurred in 955 (27%) patients in the omega-3 PUFA group and 1014 (29%) in the placebo group (adjusted hazard ratio [HR], 0.91; 95.5% confidence interval [CI], 0.833 - 0.998; P = .041).

- Death or admission to hospital for CV reasons occurred in 1981 (57%) patients in the omega-3 PUFA group and 2053 (59%) in the placebo group (adjusted HR, 0.92; 99% CI, 0.849 - 0.999; P = .009).

- To avoid 1 death, 56 patients needed to be treated for a median duration of 3.9 years.

- To avoid 1 death or admission to hospital for cardiovascular reasons, 44 patients needed to be treated for a median duration of 3.9 years,

- Gastrointestinal symptoms were the most frequent adverse effect in both groups.

- The investigators concluded that treatment with omega-3 PUFA was simple, safe, and provided a small benefit in terms of mortality and admission to hospital for CV reasons in patients with heart failure in usual care.

- GISSI-HF data on chronic heart-failure patients treated with rosuvastatin 10 mg were also presented at the ESC.

- After 3.9 years, there was no significant difference between rosuvastatin vs placebo in either time to death or time to death or admission to the hospital for CV reasons.

- Secondary end points also did not differ significantly between rosuvastatin vs placebo groups.

- These findings were consistent in all subgroups analyzed, including older patients, those with left ventricular ejection more than 40%, and those with and without diabetes.

- Treatment with rosuvastatin was associated with a 27% decrease in LDL cholesterol at 3 years, from 123 mg/dL at baseline to 90 mg/dL.

- Exploratory analysis showed no treatment effect based on achieved LDL-cholesterol reductions.

Pearls for Practice

- Omega-3 PUFA supplementation was associated with reduction in death from any cause and in death or admission to hospital for CV reasons in a large population of patients with symptomatic heart failure of any cause.

* After 3.9 years, there was no significant difference between rosuvastatin 10 mg vs placebo in either time to death or time to death or admission to the hospital for CV reasons in all subgroups analyzed, including older patients, those with left ventricular ejection more than 40%, and those with and without diabetes.