Fish Oil Cuts Heart Failure Morbidity, Mortality

BY BRUCE JANCIN
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MUNICH — Supplementation with a single daily low-dose fish oil capsule in patients with chronic heart failure resulted in modest but clinically meaningful reductions in mortality and cardiovascular hospitalization in a nearly 7,000-patient randomized trial presented at the annual congress of the European Society of Cardiology.

In a surprise finding, the same Italian study, known as GISSI-HF, concluded that rosuvastatin at 10 mg/day had no effect on mortality or hospital admission for cardiovascular events, suggesting that patients with chronic heart failure should not be started on statins. (See story below.)

In GISSI-HF, 6,975 patients with New York Heart Association class II-IV chronic heart failure were randomized in double-blind fashion to 1 g/day of omega-3 polyunsaturated fatty acids (n-3 PUFA) in the form of eicosapentaenoic acid and docosahexaenoic acid or to placebo. The participants were on standard background therapy with the agents of proven efficacy in heart failure.

All-cause mortality after a median 3.9 years of follow-up was 27% in the n-3 PUFA group and 29% in controls, for a significant adjusted 9% relative risk reduction in the n-3 PUFA group, reported Dr. Luigi Tavazzi, chair of the GISSI-HF steering committee and professor of cardiology at the University of Pavia (Italy).

The coprimary end point in GISSI-HF was death or cardiovascular hospitalization, which occurred in 57% of the n-3 PUFA cohort and in 59% of those on placebo, for an 8% relative risk reduction that did not reach statistical significance.

In all, 44 patients needed to be treated with n-3 PUFA for 3.9 years in order to prevent one additional death or cardiovascular hospitalization, whereas 56 patients needed to be treated in order to prevent one death. Those are fairly high numbers, but it's a trouble-free therapy, according to Dr. Tavazzi.

Among the nearly 5,000 patients who remained compliant with their assigned treatment for the full study duration, the n-3 PUFA benefits were more pronounced: an absolute 3% difference in mortality equating to a 14% relative risk reduction, compared with placebo, and a 12% relative risk reduction in the combined end point, he added.

There was a significant adjusted 9% relative risk reduction in the n-3 PUFA group.

DR. TAVAZZI

The benefits of n-3 PUFA supplementation were seen across the board regardless of the cause of heart failure, which was ischemia in half of subjects, dilated cardiomyopathy in 30%, and hypertension in 15%. The benefits were also consistent in the 9% who had heart failure with preserved systolic function and in the vastly greater number of patients with a low ejection fraction.

The study was undertaken in large part based upon the earlier favorable GISSI-Prevenzione trial by the same group, which showed markedly reduced mortality—mainly because of a decrease in sudden death—in patients randomized to 1 g/day of n-3 PUFA after an acute MI (Lancet 1999;354:447-55). In addition, numerous epidemiological studies have linked fish consumption to a reduced risk of cardiovascular death.

In an interview, Dr. Tavazzi attributed the high long-term compliance rate with the n-3 PUFA regimen in GISSI-HF with the simple, once-daily, 1-g dosing, which was essentially devoid of side effects.

"If you take a large population with many elderly people, who are often frail, and all of them are already on many heart failure medications, and then you prescribe the new drug forever, you need to have a very well-tolerated dose, and this was exceptionally well tolerated," he said.

Other studies of n-3 PUFA supplementation in cardiovascular medicine have used daily dosages of up to 24 g/day, with 3-6 g/day being most typical—and they've generally been brief trials that begged the issue of long-term compliance, the cardiologist continued.

"In the last 10 years or so, no new life-prolonging drugs have appeared on the scene in heart failure. The therapeutic approach to chronic heart failure has been rather static. A new drug, even if it gives only moderate benefit on top of optimal therapy, like n-3 PUFA, might be important for physicians to consider," Dr. Tavazzi added.

New ESC president-elect Dr. Michel Komajda predicted that the GISSI-HF findings could end up having a significant impact on daily practice.

"Those of us who have the responsibility to draw up the next version of chronic heart failure guidelines will pay a lot of attention to the results of the GISSI-HF trial. We will weigh on the one side that the benefit observed is modest and that the outcome curves diverge only after 2 years, but on the other side that this benefit was significant statistically, that the product is well tolerated, it is cheap, and the context is that we have very little to offer at the moment to our heart failure patients in terms of additional medications to improve their outcome," explained Dr. Komajda of Pierre and Marie Curie University, Paris.

Nevertheless, he added, there remains "a bit of mystery" regarding the mechanism of benefit, as there was no significant reduction in sudden cardiac death or presumed arrhythmic death in the n-3 PUFA group. And the optimal dosage has yet to be defined, Dr. Komajda said.

GISSI-HF was simultaneously published online (Lancet 2008 Aug. 31 [doi:10.1016/50140-6736(08)61239-8]).

The trial was funded by the Società Prodotti Antibiotici S.p.A., Pfizer Inc., Sigma-Tau Pharmaceuticals Inc., and AstraZeneca Pharmaceuticals, which provided Dr. Tavazzi with research support and honoraria. ■

Statin Therapy Offers No Benefit in Chronic Heart Failure

BY BRUCE JANCIN
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MUNICH — Rosuvastatin at 10 mg per-day had no impact on clinical outcomes in patients with chronic heart failure in a large clinical trial.

Results of the GISSI-HF trial, in which 4,574 Italian patients with chronic heart failure were randomized double blind to the statin or placebo and followed for a median of 3.9 years, suggest that there is no indication for giving statins as a treatment for heart failure, Dr. Gianni Tognoni said at the annual congress of the European Society of Cardiology.

He noted that this is the second large clinical trial that has failed to show a mortality benefit for statin therapy in patients with symptomatic chronic heart failure. The GISSI-HF trial follows the 5,011-patient Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), which featured 33 months of follow-up in a population with a history of ischemic heart disease (N. Engl. J. Med. 2007; 357:2248-61).

In GISSI-HF, all-cause mortality was 29% in the rosuvastatin (Crestor) group and 28% with placebo. The other primary end point—death or hospitalization for cardiovascular reasons—occurred in 57% of statin-treated patients and 56% on placebo, according to Dr. Tognoni, cochair of the GISSI-HF steering committee and professor of cardiology at the Mario Negri Research Institute South, Chieti, Italy. Both of the differences were statistically nonsignificant.

The GISSI-HF was a nested study designed to test two hypotheses. Unlike the statin hypothesis, the other one—that a once-daily, low-dose fish oil capsule would reduce morbidity and mortality in patients with symptomatic chronic heart failure—was supported by the findings. (See story above.) The only GISSI-HF participants in the larger fish oil study who weren't randomized to rosuvastatin or placebo were already on a statin or had a contraindication.

Discussant Dr. Philip Poole-Wilson commented that he found GISSI-HF persuasive and generalizable, particularly taken together with CORONA. The findings are surprising and disappointing in light of the much-discussed pleiotropic effects of statins, which now appear to be clinically irrelevant in the setting of heart failure.

The trials, he said, contain a valuable lesson: "GISSI-HF has refuted many observational studies, and yet again meta-analyses have been shown to be wanting. They all predicted a positive outcome. And there were even those who said that the CORONA study and this study were unethical because it was so obvious that statins would be beneficial; they were wrong," declared Dr. Poole-Wilson, professor of cardiology and head of cardiac medicine at the National Heart and Lung Institute, Imperial College, London.

The GISSI-HF trial indicates patients with symptomatic heart failure should not be started on a statin. That's obvious, he said. But the studies also raise several new controversies, he continued.

"If a patient has severe heart failure and is already on a statin, are you going to withdraw it? The trial didn't actually address that question, yet we have to make a judgment. My judgment is that the answer is probably yes," Dr. Poole-Wilson said.

Similarly, he would now be inclined not to start a statin in an asymptomatic patient with New York Heart Association class I heart failure, although that's a decision that needs to be individualized.

There is, however, overwhelming evidence that statins are beneficial in patients who have coronary heart disease but don't have heart failure.

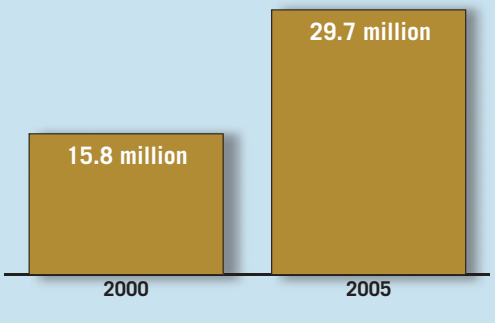
"And one of these benefits is to reduce new-onset heart failure. So all of those patients must be started and maintained on a statin," the cardiologist emphasized.

The GISSI-HF trial was funded by the Società Prodotti Antibiotici, Pfizer Inc., Sigma Tau Pharmaceuticals Inc., and AstraZeneca Pharmaceuticals, which provided Dr. Tognoni with research support and honoraria.

The GISSI-HF rosuvastatin trial was published online (Lancet 2008 Aug. 31 [doi:10.1016/50140-6736(08)61240-4]). ■

DATA WATCH

Number of People Buying Statins Increased by Nearly 88% Over 5 Years



Note: Based on prescriptions purchased in an outpatient setting.
Source: Agency for Healthcare Research and Quality