The mean age of all subjects was 76 years, and 35% were female. At baseline, 55% of all subjects had been diagnosed with kidney disease and 77% had 2 or more clinically relevant comorbidities.

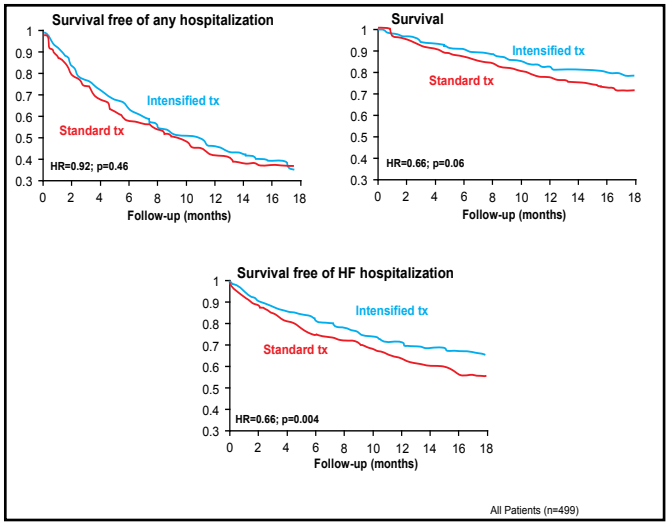
Subjects were treated according to ESC Guidelines with ACE [angiotensin-converting enzyme] inhibitors (ARB [angiotensin receptor blocker], if ACE inhibitors not tolerated), beta-blockers, and spironolactone (for persistent NYHA >III, eplerenone if not tolerated) in adequate doses.

In both the standard and intensified treatment groups at baseline, 95% of the subjects were on ACE inhibitor/ARB therapy, with 81% and 76%, respectively, also on beta-blocker therapy. In both stratified age groups, 95% of subjects were on ACE inhibitor/ARB therapy, with 84% in the younger group and 75% in the older group on beta-blocker therapy.

Dr. Brunner-La Rocca reported a significant increase in ACE inhibitor/ARB and beta-blocker doses among BNP-guided therapy subjects compared with standard treatment subjects ($p<0.001$), as well as a comparative increase in mineral corticosteroid antagonist (MCA) use ($p<0.05$) between the 2 groups. Diuretic, digoxin, and nitrate use was similar in both groups.

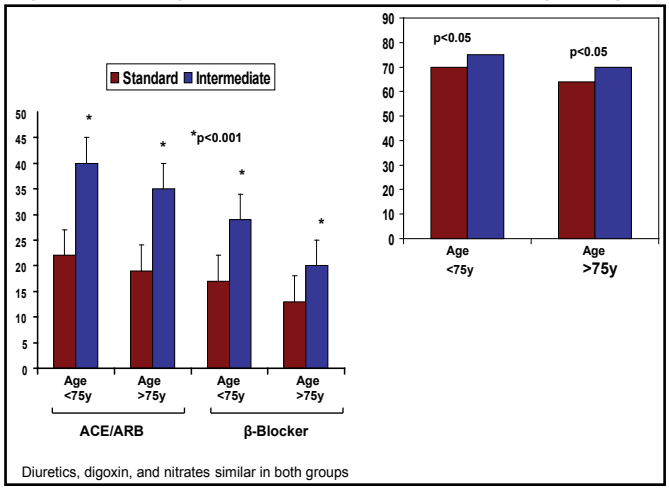
Dr. Brunner-La Rocca reported that there was no improvement by intensified BNP-guided therapy on the primary endpoint of survival free of hospitalization (HR=0.92; p= 0.46). However, he reported an improvement with intensified BNP-guided therapy on the secondary endpoints of survival (HR=0.68; p=0.06) and survival free of HF hospitalization (HR=0.66; p=0.008; Figure 1).

Figure 1. Study Endpoints. All Patients.



He also reported that when the results were stratified by age (60 to74 years vs 75 and older), there was a significant difference between the 2 age groups. Whereas there was significant improvement in survival (HR=0.38 [95% CI, 0.18 to 0.80]; p=0.01) and in survival free of HF hospitalization (HR=0.41; 95% CI, 0.23 to 0.72; p=0.002) in younger patients no effect of the treatment strategies was seen in elderly subjects (Figure 2).

Figure 2. Dosage Increase Stratified According To Age.



The quality-of-life primary endpoint showed improvement in all patients regardless of treatment. However, improvement in quality of life was significantly lower in the older (≥75 years) intensively treated patients compared with older patients on symptom guided therapy (interaction $p<0.05$).

Dr. Brunner-La Rocca concluded that this study shows that evidence from HF trials in younger patients "may not simply be applied to older patients. We need specific heart failure trials in elderly patients, and I hope that this study will stimulate further trials in this regard."

Fish Oil Supplementation—But Not Statin Therapy—Reduces Death in Heart Failure

GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – Insufficienza cardiaca) provides support for the use of fish oil supplements in patients with symptomatic heart failure (HF) but indicates no benefit of statin therapy in this patient population. Fish oil supplements reduced the risk of all-cause death or hospitalization for cardiovascular (CV) causes, while treatment with rosuvastatin had no effect on these outcomes.

The GISSI-HF program included 2 nested studies that were designed to evaluate n-3 polyunsaturated fatty acids

(PUFA) and statins among patients who received optimal medical therapy for HF. Study investigators Luigi Tavazzi, MD, Policlinico San Matteo di Pavia, Pavia, Italy, presented the n-3 PUFA results, and Gianni Tognoni, MD, Consorzio Mario Negri Sud, Chieti, Italy, reported the rosuvastatin findings, which were simultaneously published online in *The Lancet* [GISSI-HF Investigators. *Lancet* 2008].

GISSI-HF (NCT00336336) enrolled 6975 patients with chronic New York Heart Association (NYHA) class II-IV HF, regardless of etiology and with any baseline left ventricular ejection fraction. Patients were randomly assigned to treatment with n-3 PUFA 1 g daily or placebo, and those who had neither a clear indication nor a contraindication to statin therapy (n=4574) also were randomly assigned to treatment with rosuvastatin 10 mg daily or placebo. The 2 primary endpoints were all-cause mortality and all-cause mortality or hospitalization for CV events.

Benefits with Fish Oil Supplements

After a median of 3.9 years, 27.3% of patients in the n-3 PUFA group and 29.1% of patients in the placebo group died from any cause (p=0.041). After adjusting for recent HF hospitalization, prior pacemaker implantation, and the presence of aortic stenosis, treatment with n-3 PUFA reduced the relative risk (RR) of death by 9% (HR=0.91; 95% CI, 0.83 to 0.99).

Fish oil supplementation also reduced the RR of death or hospital admission for CV events by 8%, from 59.0% in the placebo group to 56.7% in the n-3 PUFA group (p=0.009). In addition, according to subgroup analyses, patients who were treated with n-3 PUFA were less likely than placebo recipients to be hospitalized for ventricular arrhythmia (2.8% vs 3.8%; p=0.013).

Low-dose n-3 PUFA was very well tolerated, with no excess in treatment discontinuations (28.7% vs 29.6% in the placebo group) or adverse events (2.9% vs 3.0%). A similar number of patients in the n-3 PUFA group (n=96) and the placebo group (n=92) reported gastrointestinal problems, the most common adverse event.

Neutral Effects of Statin Therapy

Treatment with rosuvastatin did not improve prognosis in the GISSI-HF trial. Patients in the rosuvastatin and placebo groups were equally likely to reach the endpoints of all-cause mortality (28.8% and 28.1%, respectively; p=0.660) and all-cause mortality or CV hospitalization (57.1% vs 56.1%; p=0.594). Moreover, there were no differences between the treatment groups in the endpoint components of CV mortality, sudden cardiac death, CV hospitalization, fatal and nonfatal myocardial infarction (MI), or fatal and nonfatal stroke.

Rosuvastatin failed to alter mortality despite clear pharmacologic activity, including beneficial effects on low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hsCRP), a marker of inflammation. Whereas LDL-C levels remained relatively steady in the placebo group (increasing by 7% at Year 1 and decreasing by 2% at Year 3), LDL-C levels dropped by 32% at Year 1 and remained reduced by 27% compared with baseline at Year 3 in the rosuvastatin group (p<0.001). After 3 months of therapy, the mean hsCRP level dropped by 4.6% in the placebo group and 16.6% among those who received rosuvastatin (p=0.020).

GISSI-HF joins CORONA (Controlled Rosuvastatin Multinational Trial in HF) in showing that statin therapy does not lessen the risk of death in patients with HF [Kjekshus J et al. *N Engl J Med* 2007]. Compared with GISSI-HF, CORONA evaluated an older group of patients (mean age, 68 years vs 73 years) with a greater prevalence of ischemic HF (40% vs 100%) and more severe disease (37% vs 63% NYHA III/IV). However, the findings of GISSI-HF mirror those of CORONA: rosuvastatin has a neutral effect in HF patients.

Clinical Implications

The role of statins in HF, and the clinical implications of GISSI-HF in particular, will be a source of debate within the cardiology community, said Philip A. Poole-Wilson, MD, Imperial College, London, UK. Given the findings of CORONA and GISSI-HF, Prof. Poole-Wilson argued that patients with symptomatic HF (NYHA II-IV) should not be started on statin therapy and that those who already are taking statins should have these agents withdrawn. For patients who have structural or functional defects but no HF symptoms (NYHA I), the clinical consequences of GISSI-HF are less clear.

Prof. Tognoni had a more conservative interpretation of the GISSI-HF findings. Although statins should not be given to patients with HF that is of nonischemic etiology, physicians should carefully consider the benefits of continuing or discontinuing statin therapy in patients with ischemic HF, he said. For example, discontinuing statin therapy may improve compliance with other concurrent, evidence-based treatments.

Overall, the neutral findings of GISSI-HF do not diminish the valuable role of statins in CV risk reduction. "Patients with coronary heart disease without HF must be started and maintained on statin therapy," Prof. Poole-Wilson concluded.