

Editorial

Statins or Status Quo?



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Always trying to lessen the morbidity and mortality associated with heart failure (HF), new treatment strategies are constantly being evaluated in this syndrome. Sometimes new approaches seem radical and not based directly on clearly defined pathophysiologic principles. Arguably, lowering lipid levels in patients with ischemic heart disease who also have HF makes intuitive sense. Preventing ischemic myocardial injury could be the result of pharmacologic management of dyslipidemias, and, theoretically, this might preserve ventricular function. In turn, this might attenuate HF complications. However, not all HF is ischemic in nature, and other benefits of lipid-lowering medications might be helpful in the HF milieu. The premise that statins could be beneficial in HF arose from data derived from experimental studies demonstrating favorable effects on vascular endothelium [1], angiogenesis, neurohormones, anti-inflammatory effects [2], anti-oxidant effects, and anti-arrhythmic effects. Meta-analyses, retrospective studies, and prospective studies have also suggested that statins may be beneficial in HF [3,4]. Evidence from the Treating New Targets (TNT) study [5] and Controlled Rosuvastatin Multinational (CORONA) study

[6] suggests that statins reduce the incidence of HF hospitalizations.

In a post-hoc analysis of the TNT study [5], intensive treatment with atorvastatin (80 mg) when compared with a lower dose (10 mg) in patients who had stable coronary disease (American College of Cardiology/American Heart Association [ACC/AHA] stage A HF) significantly reduced HF hospitalizations, and this benefit was observed only in patients who had a history of HF. In this study, 10,001 patients with stable coronary disease were randomized to treatment with atorvastatin, 80 or 10 mg/d, and followed up for a median of 4.9 years; 7.8% of patients had a history of HF. Systolic HF (left ventricular ejection fraction [LVEF] < 30%) and advanced HF were exclusion criteria for the study. A pre-defined secondary end-point of the study was hospitalization for HF. These investigators found that the incidence of HF hospitalization was 2.4% in the 80-mg arm and 3.3% in the 10-mg arm (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.59 to 0.94; $p = .0116$). The treatment effect of the higher dose was more marked in patients who had a history of HF: 17.3% versus 10.6% in the 10- and 80-mg arms, respectively (HR,

0.59; 95% CI, 0.4 to 0.88; $p = .009$). In patients without a history of HF, the rates of hospitalization for HF were much lower: 1.8% in the 80-mg group and 2.0% in the 10-mg group (HR, 0.87; 95% CI, 0.64 to 1.16; $p = .34$). Only a third of patients hospitalized for HF had evidence of preceding angina or myocardial infarction (MI) during the study period. Blood pressure was almost identical during follow-up in both treatment groups.

The CORONA study in heart failure found that rosuvastatin reduced the number of cardiovascular hospitalizations but did not reduce the primary outcome or the number of deaths from any cause in older patients who had systolic heart failure (ACC/AHA stage C and D HF). There were no safety problems with this drug. This study involved a total of 5011 HF patients who were 60 years of age or older with New York Heart Association class II, III, or IV ischemic, systolic heart failure. Patients who were considered to need a statin were excluded. This study was both an efficacy study and a safety study. The patients enrolled were randomly assigned to receive 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal MI, or nonfatal stroke; it was hypothesized that the primary composite outcome was reduced by 16% as in other statin trials. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. The median follow-up duration was 32.8 months.

The CORONA investigators found that, when compared with the placebo group, patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%; $p < .001$) and of high-sensitivity C-reactive protein (difference between groups, 37.1%; $p < .001$). During a median follow-up period, the primary outcome occurred in 692 patients in the rosuvastatin group and 732 in the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02; $p = .12$), and 728 patients and 759 patients, respectively, died (HR, 0.95; 95% CI, 0.86 to 1.05; $p = .31$). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group ($n = 2193$) than in the placebo group ($n = 2564$) ($p < .001$). No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group. The investigators overestimated the efficacy of statins in

reducing mortality due to HF prior to the study, resulting in a negative analysis. Although this study did not meet the prespecified efficacy endpoints, it did demonstrate that rosuvastatin is safe in HF patients. It has been suggested that the CORONA study may have shown the beneficial effects of statins in HF if the study had been conducted for a longer duration [7]. Earlier articles about statin therapy have emphasized that an important element of lipid lowering is not only “how low should the lipids go?” but also the duration of therapy or “how long should the patient be treated?” [8].

A more recent retrospective evaluation of 13,533 Medicare beneficiaries over 65 years of age who were hospitalized with HF (ACC/AHA stage C and D HF) and had preserved systolic function used the Cox proportional hazard model and found that discharge statin therapy was associated with significant improvement in 1- and 3-year mortality (risk ratio [RR] 0.69, 95% CI 0.51 to 0.78; RR 0.73, 95% CI 0.68 to 0.79, respectively) [9]. This study reported that discharge statin therapy was associated with greater survival benefits than even angiotensin converting enzyme inhibitors or beta-blockers in elderly patients who had HF and preserved left ventricular systolic function. These results are intriguing in the context of the findings of the CORONA study and suggest that the atherosclerotic process may be different in HF due to systolic dysfunction compared to patients who have preserved systolic function.

Another retrospective study reported that statins as a class improve mortality in elderly patients who have HF (ACC/AHA stage C and D HF), even when used at low doses, but the favorable effects were related to the duration of exposure to statin treatment [10]. These investigators analyzed long-term mortality in Canadian patients 65 years of age or older who were discharged from hospital with a diagnosis of congestive heart failure (CHF) from January 1998 to December 2002. The study cohort was comprised of 15,368 HF patients who were prescribed atorvastatin, simvastatin, pravastatin, or lovastatin. In this dataset, 6670 (43.4%) filled a prescription for atorvastatin, 4261 (27.7%) for simvastatin, 3209 (20.9%) for pravastatin, and 1228 (8.0%) for lovastatin. The drug dosages were relatively low, with 82% of patients receiving the agent at a dose of 20 mg or less. Controlling for time-dependent covariates representing current use and dosage, as well as for age, sex, coronary artery disease, and several other comorbidities, investigators found that

treatment with pravastatin (adjusted HR 0.94, 95% CI 0.83 to 1.07), lovastatin (adjusted HR 1.02, 95% CI 0.88 to 1.17) or simvastatin (adjusted HR 0.92, 95% CI 0.83 to 1.01) was similar in effectiveness in preventing mortality compared to atorvastatin (reference in this analysis) in this population with HF.

The rather muted findings of the CORONA study in systolic HF are perhaps due to several factors [7], including older age of the individuals and accompanying comorbidities, heterogeneity of the syndrome of HF including the so-called “obesity paradox” (in which obese patients who have HF have a better prognosis than nonobese HF patients) [11,12], and limitations of randomized clinical trials, including relatively small sample size and short duration of follow-up. In addition, the metabolism in HF is complex, with up to 68% of HF patients having muscle atrophy and several having underlying cardiac cachexia. It could be argued that, in the latter, lowering low density lipoprotein levels in HF patients who have excessive catabolism may be less beneficial than in those with normal metabolism. A better understanding of the underlying metabolic status of the HF patient is needed before we can tailor statin therapy in this syndrome with myriad clinical manifestations.

The recommendation of ACC/AHA for stage A HF includes treatment of dyslipidemia with statins. There are approximately 60 million individuals in the United States with stage A HF, and these patients should be considered for statin therapy, particularly when there is a history of MI, because treatment of dyslipidemia has been shown to reduce the likelihood of death and of HF in patients who have a history of MI [13–15]. Although the preponderance of evidence suggests that statins are safe in HF, even in the elderly, current data do not support the routine use of statins in elderly patients who have ACC/AHA stage C and D systolic heart failure—the status quo remains for the practicing clinician. However, data from the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto (GISSI-HF) study, which is enrolling HF patients who have preserved left ventricular systolic function and those who have nonischemic cardiomyopathies, may lift this status quo and give impetus to approaching heart failure with a different and, arguably, more radical approach [16].

In the end, “statin” therapy for heart failure remains an intriguing and yet-to-be completely studied therapy that will, hopefully, provide a new remedy for these patients who have such high morbidity and mortality. It is exciting that this

avenue of therapy is being so vigorously addressed at the present time.

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