Statin Therapy in Heart Failure
Is It Time for a Second Look?

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Congestive heart failure (CHF) is a common end-stage clinical presentation of coronary artery disease or 2 of its major risk factors, hypertension and diabetes mellitus. Because of this, patients with CHF are often prescribed 3-hydroxy-3-methylglutaryl coenzyme-A inhibitors (statins) that not only prevent cardiovascular events such as myocardial infarction, but also reduce the risk of incident heart failure. In concept, statin therapy could benefit patients with CHF by multiple mechanisms, including reduction in further ischemic events, decreased sympathetic activity, or improved endothelial function. However, once heart failure has developed, from either ischemic or nonischemic heart disease, the benefit of statin therapy is more controversial.

In the present issue of the Journal, Haack et al1 present a well-executed series of experiments showing that simvastatin treatment significantly improved respiratory variability and arrhythmia observed in a postinfarction rat CHF model. This improvement was associated with amelioration of enhanced peripheral arterial chemosensitivity, a major mechanism mediating periodic breathing and central sleep apnea (CSA) in CHF.2,3 Rats with CHF exhibited increased respiratory variability with reduced tidal volume and augmented ventilatory responses to hypoxia but not hypercapnia. Simvastatin mediated downregulation of the exaggerated hypoxic ventilatory response and carotid nerve discharge. These changes were associated with upregulation of Kruppel-like factor 2 and endothelial NO synthase within the carotid body and nucleus tractus solitarii, a group of respiratory neurons within the dorsal respiratory group that receive afferent input from the peripheral chemoreceptors. In essence, these findings demonstrate that the increased carotid body chemosensitivity, respiratory instability, and cardiac arrhythmias observed in CHF are ameliorated by simvastatin treatment in rats.

In CHF, periodic breathing and CSA are prevalent comorbidities4 associated with increased mortality.5,6 One mechanism mediating CSA in patients with CHF is the enhanced sensitivity of the peripheral and central chemoreceptors, resulting in augmented ventilatory responses to hypoxia and hypercapnia.2,3,7,8 Furthermore, the severity of CSA correlates with the degree of sensitivity to CO2.7 Therefore, it is surprising that in the present study, CO2 chemosensitivity remained unchanged.

Given the increased morbidity and mortality associated with CSA in CHF, could statins represent a pharmacological therapy in CHF that would be of clinical benefit? Indeed, effective treatment of CSA improves survival of patients with heart failure.6 In 1 study, patients with the highest burden of CSA9 were the least likely to have their CSA suppressed with continuous positive airway pressure therapy. If statins dampen chemosensitivity, perhaps continuous positive airway pressure–nonresponsive patients with heightened chemosensitivity may respond to continuous positive airway pressure with statin adjunctive therapy.

Given the high prevalence of CSA in heart failure and that effective treatment of CSA improves survival, one might hypothesize that statin treatment would reduce mortality in heart failure. However, 2 large randomized controlled clinical trials failed to show benefit in improving survival. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)10 and Gruppo Italiano per lo Studio della Sopravvivenza nell’ Infarto Miocardico Heart Failure (GISSI-HF)11 trials each randomized patients with CHF attributable to either ischemic or nonischemic cause to rosuvastatin or placebo, and mortality was not reduced in either study. How do we reconcile the findings of the present study with the randomized trial evidence? Interestingly, data from a meta-analysis suggest that simvastatin and atorvastatin, but not rosuvastatin, may be associated with improved survival in CHF.12 Simvastatin and atorvastatin are lipophilic statins that readily cross the blood–brain barrier,13,14 In contrast, both GISSI-HF and CORONA used rosuvastatin, a hydrophilic statin that does not cross the blood–brain barrier.13,14 It is therefore conceivable that the effects of simvastatin noted in the present study were, at least in part, mediated centrally.

Another key difference is that the present study was performed in a rat model of acute heart failure, versus the chronic CHF studied in the GISSI-HF and CORONA trials. In a subgroup analysis of patients with ischemic systolic CHF, patients with low levels of biomarkers such as N-terminal pro-brain natriuretic peptide and galectin-3, a marker of fibrosis, had a significant benefit with rosuvastatin (hazard ratio, 0.33; 95% confidence interval, 0.16–0.67).15 It could be hypothesized that the beneficial effect of this hydrophilic statin was in part related to improvement in CSA via a peripheral effect on carotid bodies decreasing hypoxic chemosensitivity or via possible antifibrotic effects. Although post hoc analysis of these studies is only hypothesis provoking, biomarkers may

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help identify a key subpopulation of patients with CHF with less advanced disease and less CSA burden who may benefit from statin therapy. Patients with a high-fibrotic burden as evidenced by high level of galectin-3 may be at too advanced a degree of fibrosis to benefit.

Altogether, it is possible that certain subgroups of patients with CHF may benefit from statin therapy and that it may matter which statin and what dose is used with regard to clinical benefit in heart failure.13,14 Identifying subgroups that may benefit, whether it be the 30% to 40% of patients with CHF with CSA or perhaps patients in an earlier stage of disease with lower CSA burden, will require careful study. In addition, mechanistic details of physiological effects in humans and animal models will require further investigation using different statins of varying lipophilicity to determine which drug to test in clinical studies. Given the key differences between the animal studies, human physiological studies, and randomized trial data, we suggest that it is too soon to give up on testing in clinical studies. Given the key differences between the animal studies, human physiological studies, and randomized trial data, we suggest that it is too soon to give up on testing in clinical studies.

Disclosures

D.J. Rader has received consulting fees from Merck and Pfizer. The other authors report no conflicts.

References

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