EDITORIAL COMMENT
The Emerging Role of Statins in the Treatment of Heart Failure*
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Several retrospective studies have suggested that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may benefit patients with ischemic and nonischemic cardiomyopathy (1–5). However, there are limited prospective data to suggest that statins are beneficial once heart failure (HF) is established (6,7). Moreover, there are theoretic concerns that the routine use of statins may be harmful in patients with HF. That is, one explanation for the observation that low circulating levels of statins might be deleterious by allowing unbound endotoxin from occurring. Theoretically, the lipid-lowering effect of statins' inhibitory effects on ubiquinone (CoQ10) synthesis, which might precipitate or aggravate HF by creating problems with mitochondrial respiration (12). Thus, the safety and efficacy of statin use in HF is not clearly known.

In this issue of the Journal, Sola et al. (13) report on the results of a prospective double-blind placebo-controlled study in which they randomized 108 patients (New York Heart Association [NYHA] functional class II to IV) with non-ischemic HF and a left ventricular (LV) ejection fraction (EF) of <35% to atorvastatin (20 mg/day) or placebo for 12 months. These authors observed that LV EF increased significantly in the atorvastatin group over the 12-month follow-up period (0.33 ± 0.05 to 0.37 ± 0.04), whereas patients in the placebo group experienced a decline in EF during the same period (0.33 ± 0.04 to 0.31 ± 0.03). In addition, the LV end-diastolic dimensions decreased significantly in the cohort of patients treated with atorvastatin (57.1 ± 5.9 mm to 53.4 ± 5.1 mm), whereas LV end-diastolic dimension increased in the placebo group (56.1 ± 5.9 to 60.3 ± 5.1). The authors further noted that there was an increase in erythrocyte superoxide dismutase activity and significant reductions in serum levels of high sensitivity C-reactive protein (hsCRP), IL-6, and the type 2 tumor necrosis factor receptor in the atorvastatin group, consistent with a decrease in oxidative stress and inflammation. In a related paper also in this issue of the Journal, Bleske et al. (14) report on a smaller study to determine the effect of aggressive statin therapy on patient safety and surrogate biomarkers for HF. These authors randomized 15 patients (NYHA functional class I to III) with non-ischemic cardiomyopathy into a double-blinded, placebo-controlled crossover trial. Patients already receiving maximal medical therapy were treated with 80 mg of atorvastatin or matching placebo for a 12-week period, with a minimum of an 8-week washout period. Bleske et al. (14) evaluated biomarkers that reflected cardiac remodeling (N-terminal-pro brain natriuretic peptide), inflammation (hsCRP), the type 1 tumor necrosis factor [TNF] receptor), and endothelial activation (vascular adhesion molecule-1, intercellular adhesion molecule-1, soluble P-selectin). Although treatment with high-dose atorvastatin was safe and resulted in a significant decrease in low-density lipoprotein (LDL) concentrations (110 ± 27 mg/dl to 55 ± 18 mg/dl), there were no significant differences between atorvastatin and placebo with respect to the surrogate biomarkers that were measured. Before addressing what these studies tell us about the potential role of statins in the treatment of patients with HF, it is useful to digress for a moment in order to discuss what is known about the biologic properties of statins, as well as the clinical effects of statins in HF that have been observed thus far.

Evidence for the beneficial effects of HMG-CoA reductase inhibitors in experimental models and clinical trials of HF. As shown in Figure 1, HMG-CoA reductase inhibitors lower plasma cholesterol levels by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway that is responsible for cholesterol synthesis. Importantly, intermediate products in the mevalonate pathway include isoprenoids such as farnesylpyrophosphate (farnesyl-PP) and geranylgeranylpyrophosphate (geranylgeranyl-PP), which have been linked to activation of downstream signaling pathways mediated by Ras and Rho, respectively. The Ras family of proteins is responsible for cell proliferation and hypertrophy, whereas the Rho family of proteins is important for superoxide generation and cytoskeletal formation (15,16). Rho inhibition has also been linked to increased expression of endothelial nitric

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**Evidence for the beneficial lipid-independent effects of statins on outcomes in coronary artery disease, as well as the broader question of whether statins should be routinely used in all patients with HF, including those with ischemic HF with low or normal LDL levels.**

**Clinical trials.** Several retrospective analyses of clinical trial databases have suggested that, for patients with coronary artery disease, the use of statins has either reduced the incidence of HF (3) or reduced the mortality of patients with known HF (24,25). Given the known salutary effects of statins on outcomes in coronary artery disease, as well as the high prevalence of ischemic heart disease in HF trials, these findings are not surprising. More interesting, perhaps, is a recent study by Node et al. (7), which provides provisional evidence for the beneficial lipid-independent effects of statins in HF patients. The authors showed that patients (n = 51) with symptomatic nonischemic dilated cardiomyopathy (NYHA functional class II to III) who were randomized to simvastatin for 14 weeks had an improvement in NYHA functional class; improved LV function; and significant decreases in circulating levels of plasma TNF, IL-6, and brain natriuretic peptide. In a smaller study, Laufs et al.

**Farnesylated proteins (Ras)**

**Squalene**

**Ubiquinone**

**Geranylgeranylated Proteins (Rho)**

**Figure 1.** The mevalonate pathway leads to the synthesis of cholesterol. Important intermediate products in the mevalonate pathway include isoprenoids such as farnesylpyrophosphate (farnesyl-PP) and geranylgeranylpyrophosphate (geranylgeranyl-PP), which have been linked to activation Ras- and Rho-mediated signaling. 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors decrease the synthesis of isoprenoids as well as cholesterol by blocking HMG-CoA reductase.

oxide synthesis, which has a beneficial effect on endothelial function through increased nitric oxide production. Although the mechanism is less clear, statins also activate the phosphatidylinositol 3-kinase/Akt pathway, which is coupled to cytoprotective signaling pathways (17). On the basis of the foregoing arguments, the lipid-independent effects of statins would be expected to be beneficial in HF patients.

**Experimental models.** Experimental infarct studies have shown that treatment with statins leads to attenuation of LV remodeling and improved LV ejection performance without directly affecting infarct size. The attenuation in LV remodeling was attributed to decreased cardiac myocyte hypertrophy, decreased activation of matrix metalloproteinases, and decreased fibrosis (18). Importantly, statins have also been shown to promote angiogenesis (19), mobilize bone marrow endothelial progenitor cells (20), result in down-regulation of angiotensin type I receptors (21), and lead to improved heart rate variability and baroreflex sensitivity (22,23), any or all of which may have additional beneficial effects on cardiac remodeling.

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**Is there sufficient evidence to warrant the routine use of statins in patients with HF?** There is substantial clinical evidence that statins reduce the incidence of HF in patients with known coronary artery disease by reducing coronary events. Moreover, the increasing use of lipid-lowering strategies in recent HF trials has not resulted in worsening outcomes for the subsets of patients treated with statins. Accordingly, the use of statins can be advocated in patients with HF with known coronary artery disease and elevated levels of LDL, as recommended by current practice guidelines. However, the broader question of whether statins should be routinely used in all patients with HF, including patients with ischemic HF with low or normal LDL levels and/or non-ischemic HF, remains unanswered. Given that our randomized clinical experience with statins in non-ischemic cardiomyopathy is limited to several small trials in which <100 patients have actually been treated, and given that we have no information with respect to the correct dose of statins to use in these patients, it is premature to
recommend the routine use of statins for all HF patients. Fortunately, there are several ongoing large-scale clinical outcome trials in HF patients (COnrolled Rosuvastatin multiNAtional trial in heart failure [CORONA], Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca [GISSI-HF] [Italian Group for the Study of the Survival in Cardiac Insufficiency], and RosUvastatiN Impact on VEntricular Remodelling lipidS and cytokines [UNIVERSE]) that should provide a more definitive answer to this important question. Although predicting outcomes of ongoing clinical trials in HF is generally fraught with peril, the results of the study by Sola et al. (13) in the current issue of the Journal, as well as the burgeoning experimental and clinical evidence supporting the safety and utility of statins in patients with advanced HF, suggest that statin therapy will find much broader applicability in the standard treatment of HF patients in the foreseeable future.

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REFERENCES


