EDITORIAL COMMENT

The Emerging Role of Statins in the Treatment of Heart Failure*

Kumudha Ramasubbu, MD, Douglas L. Mann, MD, FACC
Houston, Texas

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 may be harmful in patients with HF is that statins might be deleterious by allowing unbound endotoxin to activate immune cells to produce proinflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL]-1, and IL-6), which in turn might contribute to HF progression. 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 nonischemic 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), 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 nonischemic 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), IL-6, and the type 2 tumor necrosis factor receptor (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 know 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 farnesyIpyrophosphate (farnesyl-PP) and geranylgeranyIpyrophosphate (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 nitríc
and brain natriuretic peptide. In a smaller study, Laufs et al. NYHA functional class; improved LV function; and signif-
iability (NYHA functional class II to III) who were ran-
stats in HF patients. The authors showed that patients
recent study by Node et al. (7), which provides provisional
findings are not surprising. More interesting, perhaps, is a
statins on outcomes in coronary artery disease, as well as the
databases have suggested that, for patients with coronary
Clinical trials.

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 geranylgera-
lypyrophosphate (geranylgeranyl-PP), which have been linked to activa-
tion Ras- and Rho-mediated signaling. 3-hydroxy-3-methylglutaryl coen-
zyme 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. Al-
though the mechanism is less clear, statins also activate the
phosphatidylinositol 3'-kinase/Akt pathway, which is cou-
ped 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 metalloprotein-
ases, 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 1 receptors (21), and
lead to improved heart rate variability and baroreflex sensi-
tivity (22,23), any or all of which may have additional
beneficial effects on cardiac remodeling.

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 cardiomy-
opathy (NYHA functional class II to III) who were ran-
domized to simvastatin for 14 weeks had an improvement in
NYHA functional class; improved LV function; and signif-
ican decreases in circulating levels of plasma TNF, IL-6,
and brain natriuretic peptide. In a smaller study, Laufs et al.
(6) randomized 15 patients with non-ischemic dilated cardiomyopathy (NYHA functional class II to III) to
cerivastatin (0.4 mg) or placebo for an average treatment
period of 20 weeks. They observed that statin treatment
resulted in an improvement in quality of life and exercise
capacity that was accompanied by decreased plasma concen-
trations of troponin T, hsCRP, plasminogen activator
inhibitor-1, and TNF. Finally, in a retrospective analysis of
their cardiac transplant database (n = 551 patients), Hor-
wich et al. (1) showed that statin use was associated with
improved survival without the necessity for urgent heart
transplantation in both ischemic and nonischemic HF
(hazard ratio 0.41, 95% confidence interval 0.18 to 0.94).
Thus, the results of the present study by Sola et al. (13) are
consistent with previous observational and prospective stud-
ies that have shown beneficial effects of statins in HF
patients. Moreover, this study extends prior observations by
demonstrating that treatment with statins leads to “reverse”
cardiac remodeling and suggests (but does not prove) that
the anti-inflammatory effects of statins may be through a
reduction in oxidative stress. In contrast, the study by Bleske
et al. (14) suggests that high-dose atorvastatin for a shorter
duration of time was safe but had no effect on HF
biomarkers. Although the reasons for these discrepant
findings are not known, the most logical explanation (aside
from the small numbers of patients) is that the patient
cohort studied by Bleske et al. had relatively mild HF and
thus had minimal activation of neurohormonal and inflam-
matory systems. Indeed, as noted by Bleske et al. (14), the
biomarkers chosen were “for the most part. . .in the range
that. . .was considered normal” (14). Thus, on the basis of
the study design that was employed, one would not have
expected to have observed striking changes in the panel of
biomarkers following statin treatment. Importantly, how-
ever, there were no obvious harmful effects of high-dose
statins, despite the significant lipid lowering that was
observed.

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 guide-
lines. 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 Sopravvenienza nell’Insufficienza Cardiaca [GISSI-HF] [Italian Group for the Study of the Survival in Cardiac Insufficiency], and RosUvastatin Imp-act on VEntricular Remodelling lipidS and cytokines [UNIVERSE]) that should provide a more definitive an-swer to this important question. Although predicting out-comes 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.

Reprint requests and correspondence: Dr. Douglas L. Mann, Faculty Center, 1709 Dryden Road, BCM620, Houston, Texas 77030. E-mail: dmann@bcm.tmc.edu.

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