Treating Diastolic Heart Failure With Statins
“Phat”* Chance for Pleiotropic Benefits
Michael R. Zile, MD

Diastolic heart failure (DHF) is a significant healthcare problem.\(^1,2\) Nearly 50% of all patients with chronic heart failure have DHF. Once hospitalized for heart failure, patients with DHF have a 50% chance of rehospitalization within 6 months. Patients with DHF have a 5% to 6% yearly mortality rate. It is estimated that treating patients with DHF costs in excess of $3.5 billion/year. Despite the significant impact that DHF has on heart failure incidence, prognosis, and cost, only 1 large randomized clinical trial has been completed that examined the treatment of patients with DHF. Candesartan cilextil (Atacand) in Heart failure Assessment of Reduction Mortality and morbidity-Preserved (CHARM-Preserved).\(^3\)

The poor clinical outcomes and the limited treatment options for patients with DHF underscore the importance and uniqueness of the Fukuta et al study published in this issue of Circulation.\(^4\) In this study, the authors conclude that treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may lower both mortality and morbidity rates in patients with DHF. Enthusiasm for and clinical application of the results of this study must be tempered by the fact that this represents a “preliminary report”; however, if proven effective in large randomized clinical trials, this therapeutic approach will represent an innovation and potentially a paradigm shift in the treatment of patients with DHF.

This editorial will focus on addressing 4 questions: (1) Does hyperlipidemia contribute to the pathophysiology of DHF?; (2) Why would these authors believe that statin therapy would reduce morbidity and mortality in patients with DHF?; (3) Are their data sufficiently robust to justify the performance of more definitive studies?; and (4) Does this study provide insights that will help to develop a comprehensive management strategy for patients with DHF?

Pathophysiology of DHF
It is generally agreed that patients with chronic heart failure can be divided into 2 groups based on changes in cardiac and vascular structure and function.\(^1,2,5\) Patients with systolic heart failure (SHF) are characterized by eccentric remodeling of the left ventricle, progressive left ventricular (LV) dilation, and predominant abnormalities in LV and myocardial systolic properties. By contrast, patients with DHF are characterized by concentric remodeling of the left ventricle, normal LV systolic properties, and predominant abnormalities in LV and myocardial diastolic properties.

All chronic heart failure occurs in the context of clinical disease processes that contribute to (and may cause) its development and progression. In patients with DHF, chronic arterial hypertension, coronary atherosclerosis, and diabetes mellitus play particularly important roles.\(^1,2\) It is the long-term changes in arterial pressure, coronary blood flow distribution, and myocardial biochemistry imposed by these clinical disease processes that over time alter LV structure and function and lead to the development of the heart failure syndrome. In addition to long-term alterations, short-term changes in these and other factors may contribute to acute clinical decompensation and precipitate overt heart failure presentations. For example, increased arterial pressure, poorly controlled diabetes, decreased arterial compliance, decreased venous capacitance, anemia, and renal insufficiency may contribute to the development of acute heart failure, decreased exercise tolerance, and acute pulmonary edema in patients with DHF.

Therefore, based on the pathophysiology described above, a comprehensive plan to treat DHF should include strategies that return LV structure and function to normal, prevent or reverse the end-organ effects of underlying clinical disease processes, and control or modify factors that act to precipitate acute exacerbations of DHF.

It is difficult to imagine how statins would act to alter or normalize changes in LV structure or function in patients with DHF, but as discussed below, there is some evidence that even this may be possible. What appears more likely and easier to understand, however, is the effects of statins on underlying clinical disease processes (eg, vascular atherosclerosis) and their ability to modify factors that precipitate acute exacerbations of DHF. Thus, it is likely that statins have pleiotropic benefits, some that depend on lipid-lowering mechanisms and others that are independent of lipid-lowering effects. These pleiotropic benefits may alter a number of components of cardiovascular morbidity and mortality both related to and different from heart failure events.

*Phat is a slang term that has a positive connotation: cool, desirable, tempting.

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TABLE 1. Pleiotropic Effects of Statins

<table>
<thead>
<tr>
<th>Lipid dependent</th>
<th>Lipid independent</th>
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<tbody>
<tr>
<td>Decrease vascular atherosclerosis</td>
<td>Decrease LV mass</td>
</tr>
<tr>
<td>Decrease myocardial infarction</td>
<td>Inhibit angiotensin I-mediated cardiomyocyte hypertrophy</td>
</tr>
<tr>
<td>Decrease cerebral vascular accident</td>
<td>Alter intracellular signaling molecules that affect growth regulation</td>
</tr>
<tr>
<td>Decrease peripheral vascular disease</td>
<td>Decrease extracellular signal-related kinase (ERK 1/2) activity</td>
</tr>
<tr>
<td>Decrease LV mass</td>
<td>Decrease ERK phosphorylation</td>
</tr>
<tr>
<td>Decrease RAS membrane targeting and activation</td>
<td>Decrease oxidative stress, decrease oxygen free radicals</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>Increase arterial compliance</td>
</tr>
<tr>
<td>Decrease LV fibrosis</td>
<td>Decrease vascular atherosclerosis</td>
</tr>
<tr>
<td>Decrease inflammation (decreased C-reactive protein, interleukin-6)</td>
<td>Improve endothelial function</td>
</tr>
<tr>
<td>Decrease immune activation</td>
<td>Decrease endothelin synthesis</td>
</tr>
<tr>
<td>Alter matrix metalloproteinase activity</td>
<td>Increase nitric oxide</td>
</tr>
<tr>
<td>Decrease oxidative stress</td>
<td>Decrease morbidity and mortality in patients with diabetes and renal insufficiency</td>
</tr>
<tr>
<td>Increase arterial compliance</td>
<td>Decrease thrombosis</td>
</tr>
<tr>
<td>Decrease RAS membrane targeting and activation</td>
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Pleiotropic Effects of Statins

The beneficial effects of statin therapy can be divided (somewhat artificially) into those effects that relate to its lipid-lowering effects (lipid dependent) and those effects that may be independent of its lipid-lowering effects (lipid independent; Table 1). The benefits of statin-induced alterations in lipid profiles have been shown in a variety of populations to include a reduced incidence of vascular disease, vascular events (eg, myocardial infarction and cerebral vascular accident), and cardiovascular morbidity and mortality, which result from vascular disease. Whether these lipid-dependent benefits can be realized in patients with chronic heart failure remains an open question because in most published studies, patients with heart failure were excluded. In addition, a number of studies have shown that mortality and morbidity rates in patients with SHF are higher in patients with lower total cholesterol levels (<180 to 200 mg/dL). The cause of this survival disadvantage for lower total cholesterol levels in SHF is not clear. It is believed that lower total cholesterol levels in SHF are a marker of more severe disease as evidenced by more pronounced cardiac cachexia and more pronounced activation of the immune and inflammatory systems. Fortunately, recent studies have helped to clarify the question of statin effects in patients with SHF. These studies showed that at both low and high total cholesterol levels, the addition of a statin reduced morbidity and mortality in patients with SHF. What remains unclear from these studies in patients with SHF is the degree to which the beneficial statin effects are lipid dependent or independent.

The study by Fukuta et al is the first to examine the effects of lipid therapy in patients with DHF. In this study, patients were treated with statins according to the most recent lipid guidelines. During the study, patients who were and were not receiving statin treatment had similar lipid profiles. Baseline lipids were not predictive of morbidity and mortality during the study (W.C. Little, MD, personal communication, 2005). Because DHF is infrequently associated with the development of cardiac cachexia or profound activation of the inflammatory and immune systems, it is not expected that lower total cholesterol levels would be associated with increased morbidity and mortality rates in DHF patients. Therefore, lowering lipid levels with statin therapy is not likely to have adverse effects on patients with DHF.

The beneficial effects of statins in patients with DHF are likely to result from both lipid-dependent and lipid-independent properties. For example, in animal models of LV hypertrophy and in 1 clinical study, statins were shown to reduce LV mass and reduce LV fibrosis. This lipid-independent effect may result from mild statin-induced reduction of blood pressure, alterations in myocardial growth regulatory signal transduction pathways, changes in inflammatory or immune-mediated systems, or increased arterial compliance. Statins may alter arterial compliance by changing the composition of the vascular wall or by changing endothelial response to local and circulating vasoactive compounds and neurohormones.

It is likely that the most important benefits of statin therapy in patients with DHF are based on their lipid-dependent effects on vascular atherosclerosis. How and why these effects are important in the treatment of DHF become clear when placed in the context of the causes of morbidity and mortality in patients with DHF.

Causes of Mortality and Morbidity in DHF

A significant portion of the morbidity and mortality that occurs in patients with DHF is not directly related to the heart failure state itself. For example, vascular atherosclerosis is one important clinical disease process that contributes to the development and progression of DHF and may cause morbidity and mortality separate from that imposed by the heart failure state. Recent clinical trials and epidemiological studies have shown that in patients with DHF, as much as 20% to 30% of cardiovascular mortality can be directly attributed to vascular-related disease such as death from myocardial infarction, cerebral vascular disease, and peripheral vascular disease. A significant proportion (as much as 15% to 25%) of all-cause hospitalization (morbidity) can be attributed to vascular disease (Table 2). Therefore, treatment strategies that alter the biology and natural history of vascular atherosclerosis would be expected to affect the cardiovascular morbidity and mortality in patients with DHF. The lipid-dependent effects of statins would make them a good candidate to be incorporated in such a treatment strategy.

Altering vascular atherosclerosis can also have an impact on heart failure–related end points. Epidemiological studies
TABLE 2. Vascular Causes of Morbidity and Mortality in CHARM-Preserved

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Percentage of All Causes of Hospitalization</th>
<th>Percentage of Cardiovascular Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>1.1</td>
<td>5.4</td>
</tr>
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</table>

Event rate is calculated as events/100 patient-years. Data in the third and fifth columns represent the percentage of all incidences of hospitalization (third column) and death (fifth column) that were caused by myocardial infarction or cerebrovascular accident. Mortality data are based on adjudicated events. Morbidity data are based on the number of patients hospitalized. Myocardial infarction data represent adjudicated nonfatal myocardial infarction, cerebral vascular accident data represent nonfatal cerebral vascular accident. Data provided by J. McMurray, MD, and S. Solomon, MD, personal communication, 2005, and from Lancet. 2003;362:777; and Circulation. 2004;110:2180.

have shown that 75% to 90% of patients with SHF have a history of coronary artery disease.1,2 By contrast, coronary artery disease is present in only 40% to 55% of the patients with DHF. Nevertheless, myocardial ischemia and injury commonly contribute to the structural and functional pathophysiology of DHF. Epicardial coronary artery disease can cause ischemia and injury that leads to increased extracellular matrix collagen, replacement fibrosis, cardiomyocyte necrosis, and apoptosis in both ischemic and injured myocardium and, over time, in the remote residual myocardium. Under these circumstances, statin therapy that alters coronary vascular atherosclerosis can also alter LV structure and function and thereby reduce cardiovascular morbidity and mortality, which may be more directly related to the heart failure state itself.

In addition, even in the absence of epicardial coronary artery disease, patients with DHF may develop subendocardial ischemia or injury, which can lead to focal structural and functional changes in extracellular matrix collagen and cardiomyocyte properties. Subendocardial ischemia occurs most commonly under circumstances in which there is significant LV hypertrophy, concentric remodeling, and hypertensive heart disease. Under these circumstances, control of arterial blood pressure, peripheral vascular atherosclerosis, and arterial compliance become crucial to effective treatment strategies. Recent studies have shown that hypertension plays a crucial pathophysiological role in patients with DHF who develop acute pulmonary edema and have significant exercise limitations.18,19 Effective treatment of acute pulmonary edema and prevention of its recurrence are critically dependent on adequate blood pressure control.19 In addition, Warner et al have demonstrated that exercise intolerance is associated with, if not caused by, severe increases in blood pressure during exercise. Blunting exercise-induced hypertension can effectively and significantly increase exercise time and decrease heart failure symptoms.18

Therefore, treatment strategies that target vascular atherosclerosis and hypertension may reduce cardiovascular morbidity and mortality that is both related and unrelated to the heart failure state itself. By extension, these data suggest that other underlying clinical disease processes that either alter cardiovascular structure and function or act to precipitate heart failure decompensation (eg, diabetes, renal failure, anemia) should be treatment targets in patients with DHF.

**Limitations of Previous, Present, and Future Studies**

Fukuta et al have discussed the limitations inherent in their experimental methods in a candid, complete, and clear fashion.4 Further discussion of these limitations is not necessary except to acknowledge that this is not a definitive large, multicenter, double-blind, randomized, placebo-controlled clinical study but rather a hypothesis-generating preliminary study. The authors did, however, use a state-of-the-art analytic method (propensity matching) in an effort to correct for the bias inherent in the nonrandomized treatment assignment.

It is imperative that public agencies and private industry be encouraged to sponsor large randomized clinical trials to further investigate the value of statins in the treatment of DHF. There is little question that such studies will pose certain challenges. The data from Fukuta et al provide significant assurance that such trials are in fact feasible.3 For example, whereas some patients with DHF already have preexisting indications for lipid-lowering treatment, at least 50% of the patients with DHF in the Fukuta et al study had lipid profiles that fell below those prescribed by guidelines for treatment.4 Thus, a sufficiently large sample of reasonably homogeneous patients can be defined who would be eligible for a randomized clinical study examining the benefits of statin therapy in patients with DHF.

**Conclusions**

Fukuta et al have performed an important hypothesis-generating study.4 Their study suggests that adding statin therapy to treatment strategies in patients with DHF results in decreased cardiovascular mortality and morbidity. The mechanisms by which these benefits are achieved are likely to be multifactorial, reflecting the lipid-dependent and lipid-independent pleiotropic effects of statins. Given the important public health impact of DHF, additional randomized clinical trials should be performed to both evaluate the therapeutic potential of statins and further develop comprehensive treatment strategies for patients with DHF. Appropriate treatment strategies should attempt to return LV structure and function to normal, prevent or reverse the end-organ effects of underlying clinical disease processes, and control or modify factors that act to precipitate acute exacerbations of DHF.

**References**


**KEY WORDS:** Editorials ■ heart failure ■ statins ■ lipids
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