Statins and Chronic Heart Failure: Do We Need a Large-Scale Outcome Trial?

Henry Krum, MBBS, PhD, FRACP,* John J. McMurray, MB, MD, FRCP, FACC, FESC†
Melbourne, Australia, and Glasgow, United Kingdom

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are of proven clinical benefit in coronary heart disease, at least in those patients who do not have overt chronic heart failure (CHF). However, as there have been no prospective clinical trials of statins in CHF patients, the question arises as to whether the benefits observed in the absence of CHF can be necessarily inferred in those patients in whom CHF is established. In this review, the evidence base stating support of the use of statins in CHF is presented, as well as theoretical considerations as to why these agents may not necessarily be of benefit in this setting. The beneficial potential of statins clearly relates to their plaque stabilization properties and associated improvements in endothelial function, which together should reduce the risk of further infarction and, perhaps, the ischemic burden on the failing ventricle. Furthermore, these agents may have beneficial effects independent of lipid lowering. These include actions on neoangiogenesis, downregulation of AT1 receptors, inhibition of proinflammatory cytokine activity and favorable modulation of the autonomic nervous system. The potential adverse effects of statins in CHF include reduction in levels of coenzyme Q10 (which may further exacerbate oxidative stress in CHF) and loss of the protection that lipoproteins may provide through binding and detoxifying endotoxins entering the circulation via the gut. In support of these possibilities are epidemiologic data linking a lower serum cholesterol with a poorer prognosis in CHF. These uncertainties indicate the need for a definitive outcome trial to assess the efficacy and safety of statins in CHF, despite their current widespread, nonevidence based use in this population. (J Am Coll Cardiol 2002;39:1567–73) © 2002 by the American College of Cardiology Foundation

The discussion of the treatment of chronic heart failure (CHF) usually focuses on the treatment of the heart failure syndrome per se, often forgetting the underlying causes of CHF. In western society, this is most commonly coronary heart disease (CHD), and there is clearly a complex interplay between the effects of treatment for CHF and those for CHD. One important area where this interplay has yet to be fully worked out concerns the use of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or “statins.” In this article, we review the evidence for and against the use of these agents in patients with CHF and suggest that there is sufficient uncertainty about the effects of statins to merit a definitive morbidity/mortality clinical trial.

CHD AS THE UNDERLYING CAUSE OF CHF

Statins are of proven clinical benefit in patients with CHD, at least in those who do not have CHF (1–3). Consequently, the greatest potential benefit of statins in CHF is probably in those patients with CHD. Importantly, these patients make up the bulk of those randomized in existing trials (4–10) (Table 1). Indeed, it is highly likely that the proportion assumed to have CHD is actually an underestimation, as patients with CHF thought not to have CHD are often found to have coronary artery disease if invasive investigation is undertaken (11).

IMPORTANCE OF ACUTE CORONARY EVENTS AS A CAUSE OF PROGRESSION OF CHF

Fundamental to the proposition that statins may reduce the progression of CHF is the belief that acute coronary events (which statins reduce) contribute to this progression. There is good evidence that this is, indeed, the case.

In the Studies Of Left Ventricular Dysfunction (SOLVD), interim myocardial infarction (MI) and unstable angina increased the risk of death and of hospitalization for CHF (12) (Fig. 1). Myocardial infarction had a particularly powerful effect, more than doubling the one-year risk of CHF hospitalization from 8.6% to 20.5% (relative risk: 2.1, 95% confidence interval: 1.6 to 2.6).

A similar insight can be gained from the Scandinavian Simvastatin Survival Study (4S) (1). In the placebo group of 4S, 52% of patients developing CHF had a preceding, postrandomization, MI (i.e., in many, if not most, patients a recurrent infarction) (13). Of those not developing CHF, the proportion having an interim infarction was only 16%.
DO STATINS REDUCE ACUTE CORONARY EVENTS IN PATIENTS WITH CHF?

There are two facets to this question. First, do acute coronary events occur at a sufficiently high frequency to be impacted upon, and, second, do statins retain their anti-coronary efficacy in patients with CHF? Here the assumption is made that acute coronary events have the same pathogenesis in patients with CHF as in other CHD patients.

The first question is more difficult to answer. Recognized MIs are uncommon in CHF trials (4). This may be because infarction is more commonly fatal in patients with CHF, and death is then classified as sudden death rather than due to MI (14). There is some post-mortem evidence to support this view (15). Similarly, infarction causing worsening CHF may be misclassified by end point committees (16). It is also possible, however, that coronary disease becomes “burnt out” as CHF worsens. Thus, new coronary events are uncommon, and progression of disease occurs in other ways. In this context, it is important to note that the SOLVD data on coronary events and CHF progression is derived from pooling of both the prevention and treatment trials (12). Review of data from CHF trials and registers also suggests that angina may be more common in milder CHF and less so in patients with more advanced CHF. Overall, therefore, it is likely that acute coronary events are probably a more important mechanism of progression in patients with lesser degrees of CHF and left ventricular (LV) systolic dysfunction.

In such patients, there is evidence that statins retain their efficacy in preventing acute ischemic events. Of the three large statin secondary prevention studies (1–3), only the Cholesterol And Reduction of Events (CARE) (2) study documented left ventricular ejection fraction (LVEF). Although patients with CHF and patients with an LVEF <0.25 could not be randomized, 706 patients with an LVEF of <0.40 (and >0.25) were randomized. Pravastatin was equally effective in reducing coronary events in these patients as in patients with an LVEF of >0.40 (Fig. 2).

ADDITIONAL ANTI-ISCHEMIC BENEFITS OF STATINS IN CHF

While the primary actions of statins are undoubtedly on coronary syndromes (i.e., MI and unstable angina), reversible myocardial ischemia and myocardial hibernation may be other ischemic mechanisms through which statins might improve left ventricular function (17) and CHF clinical status. Statins can reduce “silent” reversible myocardial ischemia, though the frequency of occurrence of this is unknown in CHF and its potential pathophysiological importance speculative (18). Conversely, myocardial hibernation appears to be common in CHF, and there is growing evidence that its reversal can improve left ventricular function (19). Whether or not statins, by improving coronary endothelial function and increasing blood flow, can bring this reversal about is, of course, unknown.

Table 1. Percentage of Patients With Coronary Artery Disease as the Etiology of Their Heart Failure in Major CHF Outcome Trials

<table>
<thead>
<tr>
<th>Ischemic etiology (%)</th>
<th>MERIT-HF (4)</th>
<th>COPERNICUS (5)</th>
<th>ELITE-II (6)</th>
<th>Val-HeFT (7)</th>
<th>CHARMM Added (8)</th>
<th>OVERTURE (9)</th>
<th>ENABLE (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI (%)</td>
<td>65</td>
<td>67</td>
<td>79</td>
<td>57</td>
<td>—</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>—</td>
<td>—</td>
<td>58</td>
<td>—</td>
<td>—</td>
<td>55</td>
<td>51</td>
</tr>
</tbody>
</table>

CHARM = Candesartan in Heart Failure–Assessment of Reduction in Mortality and morbidity; CHF = chronic heart failure; COPERNICUS = Candesartan Prospective Cumulative Survival trial; ELITE II = Evaluation of Losartan in the Elderly trial II; ENABLE = Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MI = myocardial infarction; OVERTURE = Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; Val-HeFT = Valsartan Heart Failure Trial.
Effects on myocardial cellular function.

1) Following: retardation of the progression of CHF. These include the additional properties of statins may be of direct relevance in restoration of endothelial function (20) and stabilization of plaque (21), a number of coronary ischemia, namely restoration of endothelial function, ongoing pathologic ventricular remodeling is not due to further ischemic events. Therefore, the benefit of statins in this setting is unrelated to their impact on ischemia and infarction (especially, coronary artery ligation with consequent MI and subsequent pathologic ventricular remodelling).

In a murine model of CHF after MI, fluvastatin decreased mortality in these mice (32) with reductions in LV cavity dilation, myocyte hypertrophy and interstitial fibrosis. Heart failure, as assessed by pleural effusion and lung/body weight ratio, was reduced.

Similar findings were also observed with cerivastatin in a rat model of CHF after MI (33). Left ventricular dimensions and end-diastolic pressures were restored towards sham values in cerivastatin-treated animals compared with placebo. This was associated with a reduction in deposition of pathologic collagen.

It is important to note that, although the above studies utilized models of CHF induced by an initial episode of ischemia and infarction (specifically, coronary artery ligation), ongoing pathologic ventricular remodeling is not due to further ischemic events. Therefore, the beneficial impact of statins in this setting is unrelated to their impact on subsequent ischemia and supports noncoronary actions of these drugs on the myocardium.

In vivo and in vitro studies also support the use of statins in animal and cell culture models of cardiac hypertrophy (34–36). Statin therapy reduces cardiac hypertrophy in these settings and appeared to do so, at least in part, via inhibition of the renin-angiotensin-aldosterone system (34,35).

2) Neoangiogenesis. Statins have been demonstrated to induce new blood vessel growth in ischemic limbs in a manner similar to vascular endothelial growth factor (23). This may arise, at least in part, due to the ability of statins to mobilize endogenous angioblastic stem cells from bone marrow.

3) Downregulation of AT1 receptor. Atorvastatin has been shown to downregulate AT1 receptors in vascular smooth muscle cells (24). The AT1 receptor plays a key role in the progression of CHF as evidenced by the therapeutic success of blockade of the renin-angiotensin-aldosterone system in this disease.

4) Restoration of autonomic function. Congestive heart failure is associated with sympathetic activation and parasympathetic withdrawal (25). As this autonomic dysfunction is associated with an increase in sudden death, restoration of autonomic function may favorably influence this outcome. Parasympathetic activity is increased in the setting of a low saturated fat diet (26). Uncontrolled studies with statins have also been demonstrated to improve autonomic function in patients with coronary disease (27). Recently, high-dose statins have been shown to reduce sympathetic nerve activity in rabbits with pacing-induced heart failure (28).

5) Inhibition of proinflammatory cytokines. Congestive heart failure is associated with activation of a number of proinflammatory cytokines. These cytokines appear to be integral to CHF disease progression. For example, tumor necrosis factor-alpha gene expression is increased within the myocardium of the failing heart and is associated with necrosis, apoptosis and pathologic fibrosis (29). Statins have been found to reduce levels of tumor necrosis factor-alpha and other proinflammatory cytokines thought important to CHF disease progression (e.g., interleukin-6) in plasma (30) and ex vivo mononuclear cell culture of normal subjects (31).

All of the above may be important mechanisms, independent of effects on ischemia and, indeed, lipid-lowering, that may underlie the potential benefit of statins in the treatment of CHF.

ARE THERE ANY EXISTING PRECLINICAL DATA THAT STATINS ARE OF BENEFIT IN CHF?

Statin therapy has been shown to improve ventricular function in various experimental animal models of CHF, particularly those where heart failure is induced by coronary artery ligation with consequent MI and subsequent pathologic ventricular remodelling.

Figure 2. Effect of pravastatin on coronary events in patients with coronary artery disease and a left ventricular ejection fraction (LVEF) of >0.40 enrolled in the Cholesterol And Recurrent Events trial (2). CHD = coronary heart disease. White bar = placebo; shaded bar = pravastatin.

ADDITIONAL POTENTIAL EFFECTS OF STATINS (INDEPENDENT OF ANTI-ISCHEMIC EFFECTS) THAT MAY BE OF BENEFIT IN CHF

In addition to effects of statins that may directly impact on coronary ischemia, namely restoration of endothelial function (20) and stabilization of plaque (21), a number of additional properties of statins may be of direct relevance in retardation of the progression of CHF. These include the following:

1) Effects on myocardial cellular function. Lipoprotein is a prominent component of cardiac membrane regulating cell function. A high membrane cholesterol component affects the enzymes required for energy production and movement of calcium through specific channels, thus potentially adversely influencing cardiac contractility (22).

2) Neoangiogenesis. Statins have been demonstrated to induce new blood vessel growth in ischemic limbs in a manner similar to vascular endothelial growth factor (23). This may arise, at least in part, due to the ability of statins to mobilize endogenous angioblastic stem cells from bone marrow.

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ARE THERE ANY EXISTING CLINICAL DATA THAT STATINS ARE OF BENEFIT IN CHF?

Prevention of new heart failure. Lowering cholesterol with statins results in a significant reduction in mortality and cardiovascular end points in comparison with placebo in patients with relatively preserved ventricular function and both normal and higher levels of plasma cholesterol and proven coronary artery disease (1–3).

The 4S study has demonstrated, albeit in a post-hoc analysis, a significant reduction in development of subsequent heart failure in patients with preserved ventricular function at the time of entry into the study (13).

Retardation of progression of established heart failure. No large-scale clinical trial to date with statins in patients with CHD has prospectively enrolled patients with CHF (these patients have, in fact, been actively excluded), and no prospective trial of statins has been specifically conducted in patients with CHF.

Retrospective, nonrandomized, subset analyses do, however, suggest a possible benefit of statins in patients with CHF.

In the 4S study, the mortality rate in patients developing CHF was 25.5% in the simvastatin group compared with 31.9% in the placebo group (13) (Fig. 3).

In the Evaluation of Losastan In The Elderly trial II (ELITE) II study, 11% of patients were receiving statins at enrollment, and this proportion increased to 19.6% during the study. Although nonrandomized, there was a significantly lower mortality in patients receiving statins (10.6%) compared with those who were not (17.6%) (37).

Furthermore, in a small study of post-MI patients (38), those with an LVEF <40% (n = 8) had a 6 absolute % improvement in LVEF versus baseline after 12 weeks simvastatin therapy.

The Heart Protection Study (HPS), a recently reported trial of patients with or at high risk of vascular disease and a total plasma cholesterol level >3.5 mmol/l did not entirely exclude heart failure patients on entry (39). Therefore, prospective analysis of the impact of statins on this subgroup may be forthcoming in the future. There were slightly fewer deaths from heart failure in the simvastatin group compared with placebo, but this did not approach significance. Detailed information of the impact of statins on heart failure awaits further analysis (as stated earlier) as well as full publication of the HPS results.

DO PATIENTS WITH CHF HAVE SERUM CHOLESTEROL CONCENTRATIONS HIGH ENOUGH TO MERIT STATIN TREATMENT?

Whether statins have a worthwhile benefit in patients with relatively low serum low-density lipoprotein (LDL) concentrations (e.g., <3.2 mmol/l) is a controversial question. It is, however, one that is particularly relevant in CHF where patients often have lower serum cholesterol concentrations than patients with CHD and no CHF. A direct relationship has been demonstrated between plasma cholesterol level and prognosis (40). If one accepts the view that the most benefit of statins is seen in patients with a high starting LDL or total cholesterol and/or in those experiencing the greatest fall, there may not be as much to gain with this type of treatment in CHF, particularly if advanced. Alternatively, if a substantial proportion of the benefit of statins in CHF is conferred via the non–lipid-lowering (“pleiotropic”) properties of these agents, then baseline plasma cholesterol levels may not be critical.

ARE THERE POTENTIAL DRAWBACKS TO STATIN THERAPY IN CHF?

So far, it has been argued that the cholesterol-lowering and other actions of statins are potentially beneficial in CHF. Are there, however, any potential drawbacks of statin therapy in CHF?

Serum cholesterol concentration and outcome in CHF. At least two observational studies have suggested that a low serum cholesterol concentration is predictive of a worse prognosis in CHF (41,42). This effect persists after adjustment for other potentially important differences that might influence prognosis. However, among 132 patients listed for cardiac transplantation, low high-density lipoprotein (HDL) (<33 mg/dl) was the most powerful predictor of survival (69%) versus 83% if HDL >33 mg/dl (43).

The “ubiquinone hypothesis.” Ubiquinone (also known as coenzyme Q10) is a ubiquitous, lipid-soluble, micronutrient that acts as a coenzyme in mitochondrial oxidative phosphorylation. Its best known function is as a potential antioxidant. Uniquinone can also be synthesized endogenously via the mevalonate-isoprene pathway (Fig. 4) as a result of the action of HMG-CoA reductase. Not surprisingly, therefore, plasma and, possibly, tissue ubiquinone concentrations are reduced during treatment with a statin, both as a consequence of a reduction in ubiquinone-rich LDL cholesterol and inhibition of its synthesis (44). The physiologic consequences of this interaction are unknown. However, CHF is known to be a state of pro-oxidant stress.
and antioxidant properties of drug therapies have been postulated to contribute to their clinical benefit. In addition, some (but not all) reasonably well-designed clinical trials have shown that dietary ubiquinone supplementation can improve exercise tolerance in patients with CHF (46–51), raising concerns that ubiquinone depletion (via statin therapy) might have adverse clinical effects. Against these theoretical concerns, however, is the recent observation that statins may have antioxidant effects via reduction of vascular reduced nicotinamide adenine dinucleotide phosphate oxidase expression (52).

The “endotoxin hypothesis.” Lipoprotein in plasma can bind and detoxify endotoxins such as lipopolysaccharide entering the circulation via the gut. In the setting of CHF, endotoxin may be an important mediator of CHF disease progression via activation of proinflammatory cytokines such as tumor necrosis factor-alpha. It is, therefore, argued that lipid-lowering with statin therapy may enhance endotoxemia by reducing plasma levels of lipoproteins (53). This may, in turn, result in further elevation of plasma levels of proinflammatory cytokines, levels of which are strongly linked to adverse prognosis in CHF (54). In support of this hypothesis, plasma levels of lipopolysaccharide have been shown to be elevated in patients with CHF (55), although the impact of statin therapy on this parameter has not been examined in this setting.

### WHY WE NEED A DEFINITIVE TRIAL OF STATINS IN HEART FAILURE

The preceding review summarizes arguments for and against the use of statins in patients with established CHF. The most powerful argument for a definitive trial is that these agents are becoming widely used in the management of the patient with CHF, presumably mostly in those with an ischemic etiology for their disease. Only very few recent trials of systolic CHF have, however, reported baseline rates of use of lipid-lowering therapy (4,6,8,10,56) (Table 2). This is in the absence of any prospective randomized trial data addressing mortality, morbidity and/or effects on hospitalization and despite the possibility that statins could be harmful in CHF.

If it is accepted that there is a need for definitive (as opposed to surrogate) data on statins in CHF, many questions remain about the design of such a trial. These include the etiology of CHF (ischemic vs. nonischemic etiology), the severity of the disease (e.g., can patients be too sick to benefit) and the cutoff level for total and/or LDL cholesterol. These issues involve both ethical considerations as well as addressing the question of whether the putative benefits of statin therapy occur via a reduction in elevated lipid levels, anti-ischemic effects or mechanisms independent of the above. The major ethical consideration is clearly

### Table 2. Percentage Use of Lipid-Lowering Therapies in Recently Reported (MERIT-HF, BEST, ELITE-II, CHARM, ENABLE) Systolic CHF Outcome Trials

<table>
<thead>
<tr>
<th>Active drug</th>
<th>MERIT-HF (4)</th>
<th>BEST (56)</th>
<th>ELITE-II (6)</th>
<th>CHARM (8)</th>
<th>ENABLE (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class studied</td>
<td>Metoprolol CR/XL</td>
<td>II–IV</td>
<td>III–IV</td>
<td>II–IV</td>
<td>II–IV</td>
</tr>
<tr>
<td>% Lipid-lowering use</td>
<td>26</td>
<td>23*</td>
<td>11*</td>
<td>41</td>
<td>45</td>
</tr>
</tbody>
</table>

*Statin use only.

BEST = Bucindolol Evaluation of Survival Trial; NYHA = New York Heart Association. Other abbreviations as in Table 1.
whether the overwhelming benefits of statin therapy in patients with vascular disease, but without ventricular dysfunction, are necessarily able to be transferred to patients with established heart failure. The preceding review would argue strongly that this is not clearly the case.

Summary. Despite major issues in study design, as previously described, there appears to be a clear need for a definitive prospective trial of statin therapy in patients with CHF. Such a trial is of great importance given the widespread use of these agents, the uncertainty of the outcome (given both beneficial and adverse mechanistic data) and the absence of definitive prospective studies in this specific patient population.

Reprint requests and correspondence: Prof. Henry Krum, Clinical Pharmacology Unit, Department of Epidemiology and Preventive Medicine and Department of Medicine, Monash University/Alfred Hospital, Prahran Victoria 3181, Australia. E-mail: henry.krum@med.monash.edu.au.

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