Low-Density Lipoprotein in the Setting of Congestive Heart Failure: Is Lower Really Better?

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Hypercholesterolemia is a risk factor for coronary artery disease (CAD), CAD mortality, and incident heart failure (HF). Lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to reduce the risk of developing HF in patients with CAD. However, in patients with chronic established HF, hypercholesterolemia has not been associated with an increased risk of mortality. Several studies have demonstrated that higher lipid and lipoprotein levels, including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides, are associated with significantly improved outcomes in HF of both ischemic and nonischemic etiologies. In light of the association between high cholesterol levels and improved survival in HF, statin or other lipid-lowering therapy in HF remains controversial. To date, large outcome trials of statin therapy in HF of multiple etiologies have not demonstrated mortality benefit.

Introduction

Heart failure (HF) continues to be a major public health concern as HF incidence, hospitalizations, and cost continue to rise. There are approximately 670,000 new cases of HF per year in the United States in persons over the age of 45 years, with an overall prevalence nearing 6 million. Despite advances in medical and device therapy, one of five patients newly diagnosed with HF will die within 1 year [1].

Cholesterol and the Incidence of Heart Failure

Hypercholesterolemia is a well-known risk factor for the development of coronary artery disease (CAD) and CAD mortality [2]. Furthermore, CAD is a major predisposing factor for HF; over 50% of HF cases in the United States are ischemic in etiology [3–5].

Although history of myocardial infarction is considered a major risk factor for the development of HF, hypercholesterolemia is considered only a minor risk factor for incident HF according to the American Heart Association [6]. Hypercholesterolemia has inconsistently been associated with development of HF in epidemiologic studies. In the Framingham study, total cholesterol (TC) level was not significantly related to occurrence of congestive HF. However, increased TC to high-density lipoprotein (HDL) ratio predicted increased HF incidence; age-adjusted biennial incidences per 1000 for men and women, respectively, were 8.4 and 6.5 when TC/HDL ratio was less than 5.0, 12.5 and 9.5 per 1000 when TC/HDL ratio was 5.0 to 9.9, and 41.6 and 52.9 per 1000 when TC/HDL ratio was ≥ 10 [7]. An analysis of the First National Health and Nutrition Examination Survey (NHANES I) epidemiologic follow-up study [3] found that hypercholesterolemia (240 mg/dL) was associated with increased risk of HF in men but not women; on multivariable adjusted analysis, hypercholesterolemia was not found to be an independent predictor of HF.

Cholesterol Lowering and the Incidence of Heart Failure

Despite the inconsistent relationship between cholesterol and HF incidence, cholesterol lowering with 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors (statins) has been shown to prevent the development of HF in patients with CAD. Post hoc analysis of the 4444 CAD patients randomized to simvastatin (20–40 mg) versus placebo in the Scandinavian Simvastatin Survival Study (4S) [8] showed that simvastatin lowered the risk of new-onset HF; incidence was 8.3% in the simvastatin group compared with 10.5% in the placebo group ($P < 0.015$) [9]. In 4S, simvastatin therapy lowered low-density lipoprotein (LDL) on average by 35% and TC by 25% [9]. Furthermore, in The Pravastatin or Atorvastatin Evaluation and Infection Trial–Thrombolysis In Myocardial Infarction 22

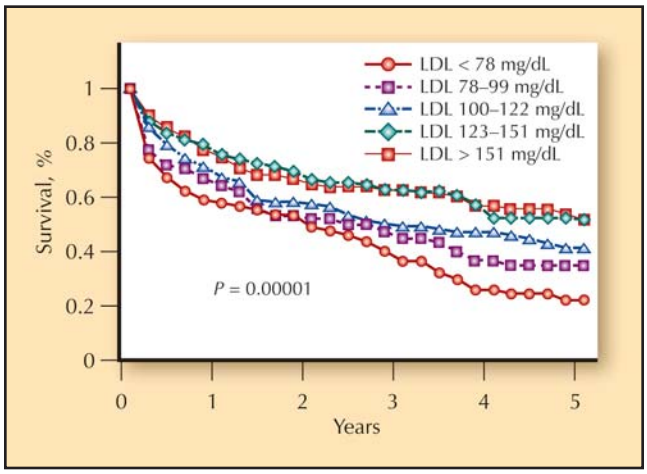

Figure 1. Five-year rates of death or urgent heart transplant by quintiles of low-density lipoprotein (LDL). (*Adapted from* Horwich et al. [12].)

(PROVE IT-TIMI 22) study [10], intensive therapy with 80 mg/d of atorvastatin compared with moderate therapy with 40 mg/d of pravastatin was associated with significantly reduced risk of hospitalization for HF in patients with acute coronary syndromes.

Lipid Levels and Chronic Heart Failure

Despite the strong correlation between high cholesterol /dyslipidemia and increased cardiovascular mortality in the general population and in CAD, higher lipid levels have consistently been associated with improved, rather than worsened, outcomes in cohorts of HF patients. The first study to document that lower TC, LDL, HDL, and triglycerides predicted higher mortality in patients with advanced HF was published in 1998 [11]. In this study of 222 advanced HF patients focused on skin test anergy, lower TC was the single best predictor of mortality among 16 variables [11]. Although this initial study received little attention, several subsequent studies confirmed the counterintuitive relationship between lower cholesterol and worsened outcomes in HF. The relationship between lipoprotein levels and mortality was described in a 2002 analysis of 1134 patients with advanced HF of multiple etiologies followed at a single university center. Low TC levels were found to be associated with characteristics known to predict worse outcomes in HF, including elevated pulmonary capillary wedge pressure, blood urea nitrogen, and creatinine, and decreased levels of sodium, albumin, and lower left ventricular ejection fraction (LVEF). Lower lipid levels were also associated with more severe symptoms of HF. Higher TC and higher LDL (Fig. 1), HDL, and triglyceride levels were significantly associated with longer survival. Less than 25% of the patients with LDL in the lowest quintile (< 78 mg/dL) survived free from the need for urgent heart transplant at 5 years compared with more than 50% for patients in the two highest quintiles (> 123 mg/dL). The inverse correlation between lipid and lipoprotein levels and survival was consistent across clinically significant patient subgroups, including those with and without CAD. On multivariable adjusted analyses for known predictors and confounders, low TC (but not LDL, HDL, or triglycerides when entered simultaneously) was found to be an independent predictor of poor outcomes. Based on receiver operator curve analysis, the best cutoff for total cholesterol was found to be 190 mg/dL, with a sensitivity of 70% for predicting mortality at 5 years [12].

Rauchhaus et al. [13,14] significantly contributed to the literature regarding cholesterol levels in HF. In a 2003 publication, this group analyzed two cohorts of HF patients (a derivation cohort in a metabolic study and a second independent group of HF patients) and also found that higher TC, LDL, and triglycerides (but not HDL) were significantly associated with improved survival. TC predicted mortality independent of other prognosticators, including cardiac cachexia, body mass index, peak oxygen consumption, and cytokine levels. LDL and triglyceride levels did not predict outcomes independent of TC. Receiver operator curve analysis identified a serum cholesterol of 201 mg/dL to be the best cutoff for mortality, similar to the 190 mg/dL described in the study by Horwich et al. [12].

The inverse association between lipid levels and outcomes has also been observed in populations of nonischemic HF patients as well as those hospitalized with acute decompensated HF [15,16]. Only one study failed to find a significant association between lipid levels and survival in a cohort of idiopathic cardiomyopathy patients, which may be due to a predominance of earlier stage HF in this study [17]. Table 1 outlines the studies of lipid levels and prognosis in HF populations published to date.

Reverse Epidemiology in Heart Failure and Other Populations

The counter-intuitive relationship between high cholesterol, a traditional cardiovascular risk factor, and improved outcomes has been termed *reverse epidemiology* [18]. Paradoxical associations between other traditional cardiovascular risk factors, including obesity and blood pressure, and clinical outcomes in HF have been described. Higher body mass index and higher blood pressure both predict better outcomes in patients with acute and chronic HF [18,19•]. Furthermore, reverse epidemiology with respect to risk factors such as body weight, cholesterol, and blood pressure, has been observed in other chronic disease populations, such as maintenance hemodialysis patients, rheumatoid arthritis, AIDS, and chronic obstructive pulmonary disease, and also in geriatric populations [19]. Common pathophysiologic underpinnings in these chronic disease states, including systemic inflammation and chronic malnutrition, may help explain the reversal of risk factors observed in these diverse populations.

Table 1. Published observational cohort studies analyzing the association between lipid levels and outcomes in heart failure

Study	Patients, *n*	Population	LVEF, %	NYHA class	Etiology	Principal finding
Vredevoe et al. [11]	222	Advanced HF at university HF center	21 ± 7	III and IV	51% ischemic, 49% idiopathic	Lower TC, LDL, HDL, and TG are independent predictors of mortality in idiopathic group ($P < 0.0001$)
Rauchhaus et al. [13]	58	Stable, nonedematous males	26 ± 3	III (53%), IV (14%)	62% ischemic	TC < 201 mg/dL is an independent predictor of mortality (RR 3.3; 95% CI, 1.05–10.58; $P = 0.04$)
Horwich et al. [12]	1134	Advanced HF at university HF center	22	III (31%), IV (63%)	48% ischemic	Multivariate RR of 0.996 (95% CI, 0.994–0.999) per 1-mg/dL increase in TC level
Rauchhaus et al. [14]	303	Consecutive HF patients at a single hospital (validation study)	30.4 ± 1.1	III (31%), IV (9%)	60% ischemic	TC < 201 mg/dL is independent predictor of 3-year survival (RR 1.97; 95% CI, 1.30–2.97; $P = 0.001$)
Christ et al. [17]	422	Marburg cardiomyopathy database	31.6 ± 10.6	II (56%), III (33%), IV (0%)	100% idiopathic	TC, LDL, HDL, and TG not found to predict transplant-free survival
Afsarmanesh et al. [15]	614	Advanced HF at university HF center	23 ± 7	IV (38%)	100% nonischemic	Low TC, LDL, HDL, and TG are univariate predictors of mortality. Lowest TC quartile RR 3.45 (95% CI, 1.78–6.70)
Horwich et al. [16]	17,791	Get With the Guidelines (HF registry of hospitalized patients)	39 ± 17	NA	56% ischemic	Lower TC, LDL, and HDL predict in-hospital mortality. Adjusted RR 0.95 (95% CI, 0.92–0.98) per 10-mg/dL increase in LDL

HDL—high-density lipoprotein; HF—heart failure; LDL—low-density lipoprotein; LVEF—left ventricular ejection fraction; NA—not available; NYHA—New York Heart Association; RR—relative risk; TC—total cholesterol; TG—triglyceride.

Potential Mechanisms for the Relationship Between Cholesterol and Mortality in Heart Failure

There are several potential mechanisms to explain the relationship between lipid levels and survival in HF. Low lipid levels may simply be markers for advanced disease and poor prognosis in HF. Low TC may be a reflection of malnutrition and cachexia, both of which are known to be associated with increased mortality in chronic HF [20,21]. Decreased lipid levels may also be a reflection of the systemic inflammatory activation characteristic of advanced HF. Both C-reactive protein (CRP) and cytokines such as tumor necrosis factor-α are upregulated in HF and predict poor prognosis in HF, and low lipid levels are closely associated with TNF and CRP [22,23].

However, as put forth by Rauchhaus et al. [13,14], low cholesterol levels may play a causative role in inducing the systemic inflammation characteristic of the advanced HF disease state. Circulating lipopolysaccharide is elevated in edematous HF patients and may be a stimulus to immune activation in HF, including activation of inflammatory cytokines. Lipoproteins such as HDL may bind endotoxin, and thus inhibit the endotoxin-stimulated elaboration of inflammatory cytokines in HF [24].

Statins as a Potential Therapy for Heart Failure

In light of the relationship between low cholesterol and high mortality in HF, a question arises regarding the use of statins or other lipid-lowering drugs in HF. An obvious potential concern regarding the use of statins in HF is the paradoxical relationship between low cholesterol levels and higher mortality in HF. However, lower cholesterol levels in HF may reflect a state of heightened inflammation, which is a potential target for the anti-inflammatory

actions of statins [24]. Another potential adverse effect of statins is that they lower coenzyme Q levels, which in theory could adversely affect cardiac function and exercise tolerance in HF patients [25].

Beyond LDL lowering, there are various potentially beneficial mechanisms of action of statins in HF patients. In patients with ischemic heart disease and HF, the anti-ischemic effects, the atherosclerotic plaque stabilizing effects, and the potential to reduce cardiovascular events are of potential benefit [26]. However, whether atherosclerotic events are a cause of morbidity and mortality in HF patients is a subject of debate. One study of autopsy data suggested that 40% of the sudden deaths and 26% of the non–sudden cardiovascular deaths in patients with systolic HF were due to acute coronary syndromes, the majority of which were not diagnosed as acute coronary syndrome–related deaths until autopsy [27]. In addition to the anti-ischemic and anti-inflammatory effects of statins, experimental data provide evidence that statins may provide beneficial actions, such as reversal of pathologic fibroproliferative myocardial remodeling, normalization of sympathetic nervous system activation, and improvement of endothelial function [26,28,29].

Is lowering LDL dangerous in HF or are the pleiotropic effects of statins beneficial in the HF population? The remainder of this review addresses the current evidence surrounding this question.

Observational Studies of Statin Therapy in Heart Failure

Several observational studies have linked statin therapy in HF to significantly improved survival. The survival benefit associated with statins in HF patients was first reported in an analysis of 551 advanced systolic HF patients (LVEF of 25% ± 7%, age 52 ± 13 years, New York Heart Association [NYHA] functional class III–IV 77%, ischemic etiology 45%) followed at a single university center [30]. Survival without urgent transplantation at 1 year was 84% in statin-treated patients and 70% in patients not treated with statins (hazard ratio [HR] of 0.45; 95% CI, 0.30–0.67). After adjustment for gender, age, medications, HF etiology, TC level, NYHA functional class, hemoglobin, creatinine, and pulmonary capillary wedge pressure using multivariate Cox regression analysis, statin therapy remained an independent predictor of improved survival at 1 year (HR of 0.41; 95% CI, 0.18–0.94).

Additional observational studies in various HF populations have also demonstrated beneficial outcomes associated with statin use. Among 24,598 adult HF patients in an integrated healthcare system in northern California, incident statin use was associated with lower risk of death or HF hospitalization in patients with and without CAD [31]. Adjusted HR for mortality was 0.76 (95% CI, 0.72–0.80) and adjusted HR for hospitalization for HF was 0.79 (95% CI, 0.74–0.85), even after adjustment for the propensity to take statins, cholesterol level, use of other cardiovascular medications, and other potential confounders [31]. A population-based retrospective cohort study of 28,828 elderly patients with new diagnoses of HF also found decreased all-cause mortality in those prescribed a statin (adjusted HR of 0.67; 95% CI, 0.57–0.78), although there was no significant reduction in risk of myocardial infarction [32]. Statins may also have benefit in patients with HF and preserved ejection fraction or in patients with diastolic HF. Fukuta et al. [33] studied 137 patients with HF and preserved ejection fraction and found, even after propensity matching, that statin therapy was associated with significantly decreased mortality and a trend toward decreased mortality plus cardiovascular hospitalizations.

Small Prospective Trials of Statin Therapy in Heart Failure

In light of the observational data on the benefits of statins in ischemic and non-ischemic HF, prospective clinical trials of statins in HF have been undertaken. The initial studies published were small in scale, with intermediate end points and not hard clinical outcomes, and were mixed in terms of findings. In an initial study by Node et al. [34] published in 2003, low dose (5–10 mg), short-term (14 weeks) simvastatin therapy in 51 idiopathic dilated cardiomyopathy patients was shown to improve symptoms, neurohormonal balance, and left systolic function. LVEF improved from 34% ± 3% to 41% ± 4% in the statin group, whereas there was no significant change in the placebo group. In the statin group, 39% had improvement in functional class compared with only 16% in the placebo group. LDL, TC, blood naturetic peptide, TNF, and interleukin-6 were significantly decreased after simvastatin treatment [34].

Two side-by-side studies published in 2006 had divergent results concerning the benefits of atorvastatin in HF [35,36]. Sola et al. [35] randomized 108 patients with nonischemic systolic dysfunction HF to 20 mg/d of atorvastatin versus placebo for 12 months. By 6 months of follow-up, the atorvastatin-treated patients had significantly higher LVEF and smaller left ventricular end diastolic and end systolic dimensions. Inflammatory biomarkers known to be associated with poor prognosis in HF (ie, TNF, interleukin-6, and CRP) were also significantly reduced in the atorvastatin group compared with the placebo group [35]. The other study, a crossover study of high-dose (80 mg/d) atorvastatin for 12 weeks (also in nonischemic cardiomyopathy patients), failed to show a significant effect of atorvastatin on inflammation, including levels of CRP and TNF. This study also found no effect of atorvastatin on endothelial function or heart rate variability, an index of autonomic balance [36]. Another study of rosuvastatin (40 mg/d) in systolic HF of both ischemic and nonischemic types showed no effect of statin therapy on ventricular remodeling, neurohormones, cytokines, or clinical outcomes compared with placebo; serum LDL was significantly lowered by 59% in the rosuvastatin

Table 2. Outline of two randomized controlled trials of statin therapy in heart failure

Study	Patients, *n*	Age, *y*	LVEF, %	NYHA class	Etiology	Primary composite end point or co-primary outcomes	Relative risk (95% CI)
Kjekshus et al. [38••] (CORONA)*	5011	Mean 73 ± 7, 41% > 75, 24% women	Systolic HF, mean 31 ± 7	II (37%), III (62%), IV (2%)	100% ischemic	Death from CV causes, nonfatal MI, and nonfatal stroke	0.92 (0.83–1.02; $P = 0.12$)
GISSI-Heart Failure Investigators [39••]*	4631	Mean 68 ± 11, 44% > 70, 24% women	Systolic and diastolic HF mean 33 ± 9, 10% > 40	II (61%), III (36%), IV (3%)	40% multiple ischemic, 35% idiopathic	1) time to death, 2) time to death or admission to hospital for CV reasons	1.00 (0.898–1.122; $P = 0.943$), 1.01 (0.908–1.112; $P = 0.903$)

*Study compared 10 mg/d of rosuvastatin versus placebo.
CORONA—Controlled Rosuvastatin Multinational Trial in Heart Failure; CV—cardiovascular; GISSI—Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HF—heart failure; LVEF—left ventricular ejection fraction; MI—myocardial infarction; NYHA—New York Heart Association.

group versus no change in the placebo group [37]. LVEF by radionuclide ventriculography improved by 3.5% in the rosuvastatin group compared with 5.3% in the placebo group ($P = 0.276$) [37].

Larger Randomized, Controlled Outcome Trials of Statins in Heart Failure

CORONA

Despite consistent benefits demonstrated in observational trials, and despite encouraging results from smaller studies of intermediate end points, large randomized controlled trials to date have not demonstrated significant survival benefit associated with the use of statins in HF (Table 2). Kjekshus et al. [38••], working with the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) group, studied 5011 patients at least 60 years of age with NYHA class II, III, or IV ischemic systolic HF in Europe and South Africa. LVEF was less than 40% in all patients and less than 35% in those with NYHA class II. Participants were on optimal HF medical therapy and were randomly assigned to receive 10 m/dg of rosuvastatin or placebo. The rosuvastatin group had LDL reduced by 35% compared with the placebo group and CRP reduced by 37% compared with the placebo group at 36 months of follow-up. However, there was no significant difference between the groups in terms of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (median follow-up of 32.8 months). These neutral results were consistent in multiple prespecified subgroup analyses. Rates of myocardial infarction were low in both the placebo and rosuvastatin groups (2.4 and 1.9, respectively). The rosuvastatin-treated participants also had similar rates compared with the placebo group in secondary end points, including 1) any coronary event (sudden death, myocardial infarction, percutaneous intervention, coronary artery bypass grafting, defibrillator shock, cardiac arrest, or hospitalization for angina); 2) all-cause mortality; 3) death from a cardiovascular event; 4) death from HF; and 5) sudden death. However, in terms of the hospitalization end point, there were significantly fewer all-cause hospitalizations (4074 vs 3694; $P = 0.007$) and HF hospitalizations (1299 vs 1099; $P = 0.01$) in the rosuvastatin versus placebo groups. There were no excess adverse events or discontinuations in the statin group [38••].

GISSI-HF

A second study of statins in HF was undertaken and published by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca (GISSI) Heart Failure Investigators [39••] in patients with symptomatic HF (NYHA II–IV) of any etiology and any degree of systolic function. If LVEF was greater than 40%, then a previous hospitalization for HF was required. Patients were already being treated with standard HF medical regimens. LDL was lowered from 122 mg/dL at baseline to 89 mg/dL at 3 years in the rosuvastatin group compared with 121 mg/dL at baseline and 118 mg/dL at 3 years in the placebo group. For the two co-primary end points of 1) all-cause mortality and 2) all-cause mortality or cardiovascular hospitalization, there was no significant difference between the rosuvastatin and placebo groups; the primary outcomes remained neutral after adjustment for potential confounders and stratification of the cohort by clinically significant subgroups. There was also no difference between the groups in terms of any of the secondary outcomes, including hospitalization for HF, hospitalization for any cause, myocardial infarction, and stroke, and there was no difference in causes of death between the groups. As in CORONA, there were no differences in adverse events between the two study groups [39••].

Discussion

Multiple cohort studies have confirmed a paradoxical relationship between cholesterol and HF survival; lower LDL and TC have not been associated with better but rather with

worse outcomes in observational studies of HF populations. Two large, randomized placebo-controlled trials have investigated the potential efficacy of statins in improving outcomes in two diverse HF cohorts. Neither study demonstrated a positive impact of statin therapy (10 mg/d of rosuvastatin in both) on primary composite outcomes, all-cause mortality, or coronary events. The coronary event rates in both populations were low, suggesting that perhaps in HF populations coronary risk reduction may no longer be important. The neutral results also suggest that the pleiotropic effects of statins in HF are either not important, not strong enough to impact outcomes, or are outweighed by a potentially detrimental effect of lowering cholesterol. On the other hand, there are limitations to the currently published clinical trials. The dose of statin used may have been too low. Although improbable, perhaps the benefits of statins in HF do not have a class effect and a statin other than rosuvastatin may be beneficial. Furthermore, in the cohort of ischemic HF patients, statin therapy lowered hospitalization rate, suggesting some mechanism of positive impact. Patients who were thought by their primary doctor to require lipid-lowering therapy were excluded from CORONA [38••].

Conclusions

In patients with HF, lower LDL is not necessarily better. Statin therapy in HF populations is safe and without risk and may have some benefit in select patients with ischemic HF. At this point, further studies are necessary to better define the role of statins and lipid-lowering agents in HF. For now, focus on implementing established, life-saving HF interventions, including angiotensin-converting enzyme inhibitors, β-blockers, and devices when indicated, is warranted.

Disclosure

No potential conflict of interest relevant to this article was reported.

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This is a large, randomized, controlled trial of rosuvastatin therapy in elderly patients with systolic dysfunction HF of ischemic etiology. The primary outcome of death and cardiovascular events was neutral between treatment groups but hospitalizations were reduced.

39. •• GISSI-HF Investigators, Tavazzi L, Maggioni AP, et al.: **Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial.** *Lancet* 2008, **372:**1231–1239.

This is a large, randomized, controlled trial of rosuvastatin therapy in patients with HF, primarily with systolic dysfunction, of both ischemic and nonischemic etiology. The two co-primary end points of mortality and mortality/cardiovascular hospitalization were similar between statin and placebo groups.