EDITORIAL COMMENT

Cholesterol and Mortality in Heart Failure: The Bad Gone Good?*

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Hypercholesterolemia is a well-established risk factor for the development of coronary artery disease (CAD) and for CAD mortality (1). Elevated serum cholesterol levels were also a risk factor for the development of heart failure (HF) in the Framingham study (2). Reduction in serum total cholesterol levels with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) in patients with CAD has resulted in a reduction in new-onset HF (3). Because CAD is a dominant etiology of HF, it would be reasonable to expect that high cholesterol would also be a risk factor and have deleterious effects for mortality in patients with established HF.

We first reported in 1998 that lower total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were predictors of higher mortality in 222 patients with advanced HF (p < 0.001) (4). Lower total cholesterol was the single best predictor of mortality among 16 variables. These results were surprising, counterintuitive, and received little attention. It was subsequently reported by Rauchhaus et al. (5) in a study of 58 chronic HF patients that a total cholesterol level <200 mg/dl predicted a poor clinical outcome (risk ratio 3.5, 95% confidence interval 1.1 to 11.0) independently of other risk factors. In this study, higher cholesterol levels were associated with lower levels of the cytokine tumor necrosis factor-alpha. The authors hypothesized that the ability of lipoprotein fractions to bind endotoxin and to serve as a natural buffer may explain the observed relationship between lower lipoprotein levels, higher cytokine concentrations, and impaired prognosis (5,6). Despite the provocative findings, these studies were limited by small sample size and short-term follow-up, leaving the relationship between cholesterol, lipoproteins, and mortality in HF far from established.

We have recently reported on the relationships of cholesterol, lipoproteins, and mortality in 1,134 patients with advanced HF of multiple etiologies (7). This study found that low total cholesterol levels were associated with characteristics known to predict worse outcomes in HF, including elevated pulmonary capillary wedge pressure, blood urea nitrogen, creatinine and decreased levels of sodium, albumin, and lower left ventricular ejection fraction. Low total cholesterol was also associated with more severe symptoms of HF. Low total cholesterol was a strong, independent predictor of increased mortality in this cohort (p < 0.00001). Patients with higher LDL, HDL, and triglyceride levels also had significantly longer survival (7). Less than 25% of the patients with total cholesterol in the lowest quintile (<129 mg/dl) survived at five years, whereas survival was >50% for patients in the two highest quintiles (≥190 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. 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 five years. This study clearly established that lower levels of total cholesterol and lipoproteins were associated with impaired survival in patients with HF, confirming the findings of the smaller, shorter-term studies (7).

In this issue of the Journal, Rauchhaus et al. (8) add significantly to the growing body of literature on this topic. They report on two cohorts of patients with chronic HF, 114 patients from a metabolic study and 303 unselected HF patients. In both cohorts, low levels of total cholesterol were associated with higher mortality rates. Lower serum cholesterol levels were also associated with higher levels of soluble TNF receptor-1 levels. Total cholesterol predicted mortality independent of cardiac cachexia, body mass index, peak oxygen consumption, and cytokine levels. Receiver operator curve analysis identified a serum cholesterol of 201 mg/dl to be the best cutoff for mortality (8). In the larger patient cohort, the probability of survival increased by 25% for each mmol/l increase in total cholesterol. This relationship was independent of age, left ventricular function, exercise capacity, and HF etiology.

Could elevated total cholesterol, which is so firmly established to be deleterious for the development of coronary heart disease and coronary heart disease mortality, actually turn out to be good for patients with chronic HF? This inverse relationship between mortality and lipid and lipoprotein levels has been observed in other disease states and populations (9–12). Critical care literature provides strong evidence for a survival advantage associated with higher lipid levels in critically ill patients. Adverse outcomes associated with low serum cholesterol have been reported in trauma, surgical illness, multiple organ failure, dialysis patients, and sepsis (9–12). Low serum cholesterol has also been associated with worsened survival in the elderly (13). With the onset of critical disease, including HF, the classic
relationship between elevated cholesterol and increased mortality no longer applies.

Investigations into the pathophysiology behind the cholesterol survival association in sepsis have focused on a role for lipoproteins in down-regulating the inflammatory immune response via an interaction between lipoproteins and bacterial lipopolysaccharide (LPS). Low-density lipoprotein and HDL have been shown to bind LPS and to protect against the immediate toxic effects of LPS on endothelial cells (14). Genetically engineered LDL receptor-deficient mice with supranormal LDL levels exposed to LPS produced fewer cytokines and survived longer than wild-type controls (15). Mice pretreated with hypolipidemic agents produced more TNF and had markedly reduced survival after being subjected to bacteria or endotoxin (16).

Similar down-regulation of inflammatory activity by lipids and lipoproteins may exist in HF patients (6). Tumor necrosis factor is elevated in HF and correlates with HF severity, and it may contribute to HF progression and cardiac injury via its proapoptotic and negative inotropic effects (17). Previous studies have also demonstrated serum LPS concentration to be increased in HF patients, with highest levels in those patients with New York Heart Association class IV (18). The protective role of lipoproteins in HF may stem from an ability to diminish the LPS-induced elaboration of cytokines detrimental to the heart, such as TNF.

Alternatively, it is possible that low cholesterol is merely a consequence of HF and has no pathophysiologic role. Lower total cholesterol levels may reflect patients with greater activation of neurohormones and/or those who are under greater metabolic demands. It is also possible that low cholesterol portends poor prognosis because low cholesterol is a marker for poor nutritional state or cachexia, states that are associated with poor HF outcomes (19). Total cholesterol, however, predicts outcome independent of cachexia, body mass index, and other variables associated with the malnourished state, and therefore cachexia alone cannot fully explain these observations (7,8).

What are the practical implications of this research? First, these studies have identified serum total cholesterol, a widely available, inexpensive, and non-invasive test, as providing independent risk prediction for mortality in patients with chronic HF. Heart failure patients with total cholesterol levels of <190 to 200 mg/dl are at 1.5 to 3 times the risk of dying as those with higher levels of total cholesterol (7,8). There are a number of intriguing mechanisms that may account for these observations and, if further clarified, could provide insight into the pathophysiology of HF (7,8). Further investigation into the mechanisms to account for this relationship is clearly needed.

The implications from a treatment standpoint are less clear. As previously discussed, this research has not established whether low cholesterol is merely a prognostic marker or is playing a causative role in mortality. Before accepting that lipid-lowering medications would be harmful in HF, studies demonstrating that reducing total cholesterol levels resulted in increased mortality would be necessary (7). There are likely significant differences in biologic effect from untreated, intrinsically low cholesterol levels as compared with the effect of pharmacologically induced reductions. As such, the results of these observational studies should not necessarily be interpreted as scientific justification to avoid the use of lipid-lowering medications in patients with HF who have other indications for treatment (7). It has been preliminarily reported that the use of HMG CoA reductase inhibitors (statins) is associated with a significantly improved survival in chronic HF patients with ischemic and non-ischemic etiologies, irrespective of baseline total cholesterol levels (20,21). Ongoing randomized clinical trials of statins in patients with HF will provide important insights into the benefits and risks of statin therapy in HF and further define the relationship between cholesterol levels and outcomes in HF (22).

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