# Statin-Mediated Low-Density Lipoprotein Lowering in Chronic Congestive Heart Failure

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**Abstract:** Many theories and clinical trials have attempted to address the effect of low-density lipoprotein (LDL) lowering in chronic congestive heart failure (CHF). The current evidence suggests that there is no convincing reason for administering statins to patients with nonischemic heart failure. Although they do not reduce the mortality rate, statins reduce LDL cholesterol and may provide some benefit to patients with ischemic heart failure. In contrast, some authors believe that statin therapy may actually worsen outcomes in patients with CHF, especially if there is excessive reduction in LDL cholesterol. This review discusses the theories attempting to link the adverse effects of statin-mediated LDL lowering in CHF to increased levels of endotoxin or reduced levels of coenzyme Q10. In addition, the 2 largest randomized, double-blind, placebo-controlled clinical trials (CORONA and GISSI-HF) were discussed. It is clear that more trials are needed to definitely ascertain the effect of statins on CHF.

**Key Indexing Terms:** Cholesterol; Coenzyme Q10; Cytokine; Endotoxin; Heart failure; Statins. **[Am J Med Sci 2014;347(1):14–22.]**

In the United States, an estimated 5.7 million Americans ≥20 years of age are suffering from chronic congestive heart failure (CHF). Approximately 50% of people diagnosed with heart failure (HF) will die within 5 years.[1] To improve this poor prognosis, we need to further comprehend the pathophysiology of HF and to modify our ways of management.

Many theories and clinical trials have attempted to address the effect of low-density lipoprotein (LDL) lowering in chronic CHF. The focus of our review is to discuss and address the role of statin therapy in patients with CHF.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and have been used for years in cardiovascular disease, owing to their cholesterol-lowering effect. Hypercholesterolemia is a worldwide problem and an established major risk factor for the development of coronary heart disease. Statins have a well-known positive effect on prevention of primary and secondary CHD.[2,3] This effect is attributed to their anti-inflammatory, antioxidant, antiatherogenic and plaque stabilization properties.[4] In fact, the anti-inflammatory effect of statins was unequivocally shown in the JUPITER trial,[5] where the observed benefit associated with the use of rosuvastatin was above and beyond what it would be expected simply from the achieved reduction of LDL cholesterol. Proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α) were identified as contributors to the syndrome of CHF[6] and to the underlying cardiomyopathic processes of adverse left ventricular remodeling and progressive left ventricular dysfunction.[7,8] The deleterious effects of proinflammatory cytokines on the cardiovascular system in the setting of CHF are described in Table 1. Because of this detrimental role of proinflammatory cytokines, "the cardioinflammatory response to heart failure" was proposed as a new HF paradigm with implications for both prognosis and treatment.[9] It has to be noted that the metabolic syndrome, a further extension of which is nonalcoholic fatty liver disease, is also strongly associated with chronic inflammation and it is linked to early atherosclerosis.[10–14] Thus, the combined anti-inflammatory and antiatherogenic action of statins could potentially provide a rationale for their use in CHF, although the possibility of drug-induced liver injury, especially in view of the rather frequent presence of congestive hepatopathy in CHF, should always be kept in mind.[15,16] However, 2 large studies, the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Heart Failure) and the CORONA (Controlled Rosuvastatin Multinational Trial), as well as some earlier smaller studies, have indicated that statins might not be as useful in patients with CHF, and in certain circumstances, they may be potentially harmful. This is possibly because of their direct adverse effect on the failed heart or it may be related to the low total cholesterol levels observed in patients with CHF, as well as other disease states and populations.[17–20]

## THEORIES

### Endotoxin-Lipoprotein Hypothesis

Rauchhaus et al[21] described the endotoxin-lipoprotein hypothesis, which suggests that the increased mortality seen in patients with CHF with low cholesterol levels might occur because there is less serum lipoprotein to bind lipopolysaccharide (also known as endotoxin), which is then absorbed from the gastrointestinal system. The absorbed endotoxins precipitate a cascade of events consisting of mesenteric venous congestion, bowel-wall edema, intestinal bacterial translocation, endotoxin release into the circulation and subsequent immune activation. This may in turn result in further elevation of plasma levels of proinflammatory cytokines, which are strongly linked to adverse prognosis in CHF.[22] In particular, TNF-α, a major proinflammatory cytokine, the levels of which are increased in CHF and in the presence of high endotoxin levels, has been shown to further decrease the LDL plasma concentrations by increasing the clearance of LDL particles from the circulation. In addition, more importantly, TNF-α is likely to induce changes in LDL composition that eventually increase atherogenicity.[23] These changes may include:

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*Submitted July 9, 2012; accepted in revised form September 6, 2012.*

*There are no conflicts of interest to disclose.*

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TABLE 1. Deleterious effects of the inflammatory cytokine cascade in congestive heart failure

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| I. Cardiac |
| Promotion of left ventricular remodeling |
| Depression of cardiac contractility |
| Cardiomyocyte hypertrophy |
| Cardiomyocyte apoptosis |
| Cardiac fibrosis |
| II. Endothelial |
| Progression of atherosclerosis |
| Oxidative stress |
| No impairment |
| Endothelial cell apoptosis |
| III. Skeletal muscular |
| Decreased skeletal muscle blood flow |
| Inhibition of proteinosynthesis |
| Skeletal muscle cell apoptosis |
| Cachexia |

- A decrease in particle size, resulting in an increased proportion of small dense LDL particles.
- An increase in the concentration of secretory phospholipase A2. The isoenzymes of secretory phospholipase A2 promote atherosclerosis by mechanisms that include lipoprotein modification, retention and oxidation, whereas its inhibition results in a significant reduction of small LDL particles and improvement of the atherogenic profile.[24]
- An increase in the LDL content of sphingolipids, including sphingomyelin and ceramide.

Furthermore, TNF-α also causes a reduction in high-density lipoprotein (HDL) plasma concentrations.[23] Thus, a vicious cycle may be established, where low cholesterol levels lead to an increase in the concentration of proinflammatory cytokines, which in turn lead to further reduction of cholesterol levels and increased atherogenicity. Some authors believe that statin therapy may enhance this deleterious effect by further lowering LDL levels.

This hypothesis, however, fails to accommodate certain clinical and experimental observations: It has been shown that in patients with CHF without peripheral edema, there was no elevation of endotoxin or TNF-α levels.[25,26] However, elevations in plasma cytokines have been observed in the New York Heart Association (NYHA) functional class II patients with CHF,[27] most of whom do not have peripheral edema. Patients with prominent right HF because of pulmonary hypertension or constrictive pericarditis have not been shown to have significant elevations of plasma cytokines. After diuretic treatment, there was a fall in endotoxin levels but no change in plasma levels of IL-6 or TNF-α.[20,25,26,28]

*Myocardial cytokine production* is another hypothesis that may directly explain the elevated cytokines in patients with CHF without implicating the low LDL levels. According to this hypothesis, elevated left ventricular diastolic wall stress induces myocardial expression of TNF-α.[7,8] However, this hypothesis also has limitations.[29]

### Coenzyme Q10

Coenzyme Q10 (CoQ10—ubiquinone) is a mitochondrial coenzyme found in all cells, which is essential for the production of ATP via mitochondrial oxidative phosphorylation.[30] Being at the core of cellular energy processes, it assumes importance in cells with high energy requirements, such as the cardiac cells, which are extremely sensitive to CoQ10 deficiency induced by certain diseases. CoQ10 has thus a potential role for prevention and treatment of heart ailments by improving cellular bioenergetics. In addition, it has an antioxidative, free radical scavenging and vasodilator effect, all of which may be helpful in these conditions. It inhibits LDL oxidation and thus the progression of atherosclerosis. It decreases both proinflammatory cytokines and blood viscosity, which is a beneficial effect, especially in patients with CHF and coronary artery disease (CAD). Recently, it has been found to be an independent predictor of mortality in CHF. Further research is ongoing to more definitely establish its role in the treatment of cardiovascular diseases.

The possible mechanisms of action of CoQ10 include:

- Improvement of cardiac bioenergetics.
- Direct free radical scavenger and antioxidant effect.

  CoQ10 must be reduced to ubiquinol, denoted QH2, to yield its maximum antioxidant activity.[31] In its reduced form (ubiquinol), the CoQ10 molecule holds electrons loosely and will quite easily give up 1 or 2 electrons to neutralize free radicals.

- Decreased concentration of atherogenic small LDL particles.

  In its reduced form (ubiquinol), CoQ10 has been shown in a recent study to exert a pronounced small LDL particle–reducing effect.[32]

- Improved endothelial function and vasodilatory effect.

  A recent study showed improvement in the endothelial relaxation with coenzyme Q10 administration. This might be related to its capability of enhancing endothelial function by counteracting nitric oxide oxidation.[33]

- Direct membrane-stabilizing activity because of phospholipid-protein interactions.

  The membrane-stabilizing property of CoQ10 has been postulated to involve the phospholipid-protein interaction that increases prostaglandin (especially prostacyclin) metabolism. It is thought that CoQ10 stabilizes myocardial calcium-dependent ion channels and prevents the depletion of metabolites essential for ATP synthesis.

- Decreased blood viscosity and improved blood flow to cardiac muscle in patients with ischemic heart disease.[34]
- Preservation of myocardial $Na^+$-$K^+$ ATPase activity and stabilization of integrity of $Ca^{2+}$-dependent slow channels.
- Correction of mitochondrial "leak" of electrons during oxidative respiration and induction of NAD(P)H: quinone acceptor oxidoreductase (DT diaphorase).
- Possible effects on prostaglandin metabolism, antiviscosity effect and altering the immune response.

## ROLE OF CoQ10 IN CHF

### Deficiency in CHF

CHF is often characterized by an energy depletion status that has been associated with low endogenous CoQ10 levels. Its levels are depleted in both serum and myocardial tissue samples of patients with chronic CHF.[35] Its deficiency may well be a primary etiologic factor in some types of heart-muscle dysfunction, whereas in others, it may be a secondary phenomenon. Whatever the case may be, CoQ10 deficiency is a treatable condition in these otherwise hopeless predicaments. The possible usefulness of the CoQ10 in the treatment of CHF may be