

Are Statins Beneficial in Heart Failure?

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Since the pioneering 4S study (Scandinavian Simvastatin Survival Study)¹, published in 1994, demonstrating the effectiveness of simvastatin in reducing all-cause mortality and coronary events in a population of patients with angina pectoris or previous myocardial infarction, other large-scale trials have confirmed the beneficial effects of hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) both in primary and secondary prevention of cardiovascular events².

Observational studies have already shown the strong correlation between coronary artery disease and hypercholesterolemia. Cholesterol reduction, particularly the LDL-cholesterol fraction, accounts, to great extent, for the mechanism by which statins delay or even block the atherosclerotic process. However, evidence suggests that statins exert several pleiotropic effects that can contribute to their potential benefit, such as enhancement of endothelial function and decrease in oxidative stress and in inflammatory activity, among others. The use of statins based on these pleiotropic effect is now being thoroughly investigated.

High-sensitivity CRP (hs-CRP) is an inflammatory marker that has been used to further improve accuracy in detecting subjects at higher risk of experiencing cardiovascular events, even those apparently healthy and with low LDL-cholesterol levels. There is evidence that the antiinflammatory effects of statins are translated into hs-CRP decrease. Nevertheless, it is still unclear whether statin therapy aiming at reducing hs-CRP may translate into decreased cardiovascular events in a population of patients with low LDL-cholesterol but elevated hs-CRP levels as a primary prevention. The JUPITER study, currently underway, is addressing this question. Statins also seem to decrease perioperative cardiac and vascular events in patients undergoing vascular surgery³. Other studies have suggested that statins are likely to have beneficial effects on the management of sepsis, based on their influence on inflammatory and coagulation cascades.

There is a specific population of patients in whom the use of statins still raise debates and doubts, namely, those with heart failure (HF). Heart failure is a syndrome characterized by a series of hemodynamic and neurohumoral changes, in addition to resulting in endothelial dysfunction and elevation of inflammatory markers. It seems natural that the pleiotropic

effects of statins might be beneficial in heart failure patients. Some clinical trials appear to confirm this hypothesis, while other experimental models do not. The purpose of this viewpoint is to discuss the evidence for or against statin therapy in the management of heart failure. It should be kept in mind that HF has different etiologies and that statin effect may differ depending on the HF *etiology*. It is known that the higher the risk of cardiovascular event the greater the benefit from statins; for example, in HF patients with diabetes and hypertension, statins will be more effective than in those without these risk factors.

Why would statins be more beneficial in HF patients?

At present, ample evidence exists that heart failure pathogenesis involves several inflammatory mediators that contribute to cardiac remodeling. Some studies have demonstrated increased levels of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 β , and interleukin-6, in HF patients. Therefore, one of the lines of research in the management of heart failure involves the greater understanding of its immunopathogenesis, in order to improve immunomodulatory disorder treatment.

1) The beneficial role of statins in HF may be explained by its antiinflammatory effects. In this respect, Mozaffarian et al⁴ conducted a randomized, double-blind, placebo-controlled clinical trial with 22 HF patients (20 of them with nonischemic HF) to evaluate the effect of atorvastatin 10 mg on their levels of systemic inflammatory markers during the 16-week treatment. No elevation in creatine phosphokinase (CPK) or liver enzymes exceeded three times the reference value. Absolute and percentage changes in the assessed inflammatory markers were as follows: decrease in tumor necrosis factor receptor-1 by 132pg/ml ($p = 0.04$) and 8% ($p = 0.056$), in hs-CRP by 1.6mg/L ($p = 0.006$) and 37% ($p = 0.0002$), and in endothelin-1 by 0.21pg/ml ($p = 0.007$) and 17% ($p = 0.01$). A post-hoc analysis revealed that the decrease in tumor necrosis factor receptor-1 was greater in patients with higher baseline levels. Statin therapy failed to decrease the levels of other inflammatory markers, including interleukin-6 and atrial natriuretic peptide⁴. The study conducted by Tousoulis et al⁵, which included 38 male patients with ischemic heart failure, showed a decrease in serum levels of interleukin-6, tumor necrosis factor- α , and vascular cell adhesion molecule-1 in the group receiving atorvastatin 10 mg/day during four weeks. This effect was not observed in the other two groups: placebo and atorvastatin 10 mg plus vitamin E⁵.

2) There is evidence that HF patients have endothelial dysfunction, which may contribute to an increase in both vasomotor tone and vascular remodeling. This change

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in endothelial function may be explained by several mechanisms, among them: a) increased cytokine levels, thereby downregulating NO synthase expression; b) disorders in the endothelium-receptor signal transduction pathway and c) enhanced angiotensin-converting enzyme activity, resulting in increased bradykinin degradation⁵. The same clinical trial conducted by Tousoulis et al⁵, mentioned earlier, has also studied the effect of atorvastatin on endothelial function, as assessed by plethysmography. In the group receiving atorvastatin 10 mg/day a significant increase in blood flow occurred after reactive hyperemia ($p < 0.05$), in addition to an increase in flow percentage (HR%) ($p < 0.01$). In the group receiving atorvastatin 10 mg/day plus vitamin E, however, only HR% increased significantly ($p < 0.05$); in this group, no significant change was found in the absolute value of post-reactive hyperemia blood flow⁵. These same authors published another study evaluating 35 HF patients (25 of them with ischemic HF), who were randomly assigned to two groups: atorvastatin 10 mg/day and no statin⁶. Endothelial function was also assessed using plethysmography. No significant change was found from baseline to post-reactive hyperemia blood flow in either group; yet HR% increased in the statin group ($p < 0.01$), but not in the non-statin group. Endothelial function improvement provided by statins had already been assessed in other populations, and the same seems to hold true for HF patients. Statins may exert their endothelial protective effect by removing superoxide anion, upregulating endothelial nitric oxide synthase (eNOS) or downregulating endothelin-1 excretion⁷.

3) In heart failure, overall adrenergic activation occurs, as well as a decrease in parasympathetic nerve activity. Statins exert their effect by normalizing the autonomic function and sympathetic outflow. In an experimental model of heart failure, rabbits with HF induced by pacing-elicited tachycardia were divided into three groups: no statins, low-dose simvastatin and high-dose simvastatin. Renal sympathetic nerve activity (RSNA) did not differ between the high-dose simvastatin group and that of normal rabbits ($p = \text{NS}$), while the other groups showed increased activity ($p < 0.05$). In addition, evidence suggests that simvastatin may enhance autonomic tone by improving heart rate variability.

4) Some experimental studies have demonstrated that post-natal neovascularization does not occur only by proliferation of already existing vessels, but also involves the contribution of bone marrow-derived endothelial progenitor cells⁸. Evidence has emerged that statins might improve endothelial progenitor cell mobilization, thereby contributing to ventricular remodeling. An interesting study conducted by Landmesser et al⁹ has demonstrated that nitric oxide synthase (eNOS) seems to play a key role in the mechanism by which statins would mobilize progenitor cells. These authors studied wild-type mice (WT) and e-NOS-deficient mice (e-NOS^{-/-}) with extensively induced anterior myocardial infarction and administered atorvastatin or placebo during four weeks to both groups. They found that wild-type mice receiving atorvastatin showed improved endothelial progenitor cell mobilization and myocardial neovascularization, in addition to a lesser degree of ventricular dysfunction and interstitial fibrosis. All these phenomena did not occur in eNOS-deficient mice receiving atorvastatin.

Why would statins be deleterious in HF patients?

There is evidence that in some severe diseases, such as sepsis, burns and trauma, low serum cholesterol is associated with worse prognosis. Horwich et al¹⁰ studied a cohort of 1134 patients referred to a university medical center for transplant evaluation in order to correlate the lipid profile with the HF prognosis¹⁰. Seventy-six percent were men, and ages ranged from 16 to 82. Heart failure etiologies were ischemic in 48%, idiopathic in 40%, and valvular in 4.5%; the remaining (7.5%) included alcohol-induced, hypertrophic, and postpartum cardiomyopathy. Only 14% of the patients were on lipid-lowering drugs. Follow-up period was 5 years. Total cholesterol (TC), LDL-C, HDL-C, and triglycerides were divided into quintiles. After gender and age adjustment, TC in the lowest quintile was associated with higher risk of death or urgent heart transplantation. Even after a multivariate analysis including age, gender, left ventricular ejection fraction, body mass index, use of ACE inhibitors, lipid-lowering drugs, pulmonary capillary pressure, blood urea nitrogen, creatinine, albumin, hypertension, diabetes, and cigarette smoking, TC was the single plasma lipid component that remained as an independent predictor of mortality or need for urgent heart transplantation. Based on a ROC (receiver operating characteristic) curve analysis, the best cut-off point for TC was 190mg/dL, with 70% sensibility to predict five-year mortality. Therefore, these authors concluded that low serum TC is seen in advanced HF patients with worse prognosis. However, we cannot say that low serum TC accounts for this worse prognosis, but rather that is very likely secondary to heart failure.

One of the hypotheses that might explain possible deleterious effects of statins is based on serum endotoxin elevation, which may contribute to heart failure progression. It has been postulated that high cholesterol levels may be beneficial in heart failure patients, because cholesterol-rich lipoproteins bind and neutralize the detrimental effects of bacterial lipopolysaccharides. Lipopolysaccharides can cross the intestinal wall in patients with advanced heart failure, stimulating proinflammatory cytokine production¹¹.

Co-enzyme Q10 (2,3 dimethoxy-5 methyl-6 decaprenyl benzoquinone) is a fat-soluble, vitamin-like quinone best known as ubiquinone, CoQ, and vitamin Q10, which is related to energy metabolism. Coenzyme Q10 is very important for the proper transfer of electrons within the mitochondrial oxidative respiratory chain, whose primary function is adenosine triphosphate production (ATP). Moreover, it seems to increase ATP levels by preventing the loss of the adenine nucleotide pool from cardiac cells. It has also been demonstrated that coenzyme Q10 can prevent lipid peroxidation by acting as an antioxidant. Earlier clinical trials showed that coenzyme Q10 supplementation may be advantageous to heart failure patients, improving symptoms and reducing the number of hospitalizations; yet, more recent studies have failed to demonstrate this beneficial effect. At any rate, it has already been demonstrated that HF patients have coenzyme Q10 deficiency, the degree of which is related to heart disease severity. Evidence exists that statins decrease coenzyme Q10 levels and, therefore, may be harmful for HF patients.

To make this issue even more controversial, Strey et al¹²

studied 24 patients with symptomatic heart failure (NYHA functional class II-III) and ejection fraction < 40% who were randomized to atorvastatin 40 mg or placebo for six weeks, at the end of which the groups were crossed-over. Their purpose was to evaluate both endothelial function by plethysmography and coenzyme Q10 levels at the end of the intervention. Significant improvement occurred in endothelial function in the atorvastatin group, and this phenomenon was significantly correlated with coenzyme Q10 reduction. In addition, although a significant correlation was found between coenzyme Q10 and LDL-C reductions ($p = 0.017$), the multivariate analysis adjusted for LDL-C decrease revealed that coenzyme Q10 reduction remained associated as predictor of statin-related endothelial function improvement. These authors hypothesized that coenzyme Q10 reduction, afforded by statins, may limit the maximal beneficial effects of these drugs on microcirculation and, going a step further, that coenzyme Q10 reduction may be a biomarker of statins pleiotropism¹².

Clinical endpoints of statin therapy in HF of different etiologies

Statins and ischemic cardiomyopathy

There is evidence that statins lower the risk of patients with coronary artery disease (CAD) progress to heart failure. In the 4S trial, 4444 CAD patients with no evidence of heart failure were randomized to receive placebo ($n = 2223$) or simvastatin 20-40 mg ($n = 2221$) and followed up on for more than five years. Among the patients in the placebo group, 228 (10.3%) developed heart failure during the follow-up period, compared with 184 (8.3%) in the statin group ($p < 0.015$)¹³.

Another prospective study randomized 486 nondyslipidemic patients in the immediate post-AMI period to receive any available statin ($n = 241$) or no statin at all ($n = 245$) for 24 months. Incidence of heart failure requiring hospitalization was lower in the statin-treated patients (1 vs 9, $p = 0.0154$).

Horwich et al¹⁴ followed-up a cohort of 551 patients with heart failure, 49% of them of ischemic etiology. Statin use was not randomized, but rather defined by each patient's physician. Most patients were on atorvastatin (28.1%). Patients in the statin group were significantly older and predominantly male, with higher rates of hypertension, diabetes, and cigarette smoking. In the ischemic group, the endpoint mortality and need for urgent heart transplantation was significantly lower in the statin group (81% vs 63%, $p < 0.001$) during the one-year follow-up¹⁴. Interestingly, despite its small number of patients ($n = 202$), studies showed significant improvement in the ejection fraction of HF patients (EF < 40%) who underwent percutaneous coronary intervention (PCI) for acute myocardial infarction and received statin (simvastatin 40 mg/day), compared with the non-statin group (31% to 42% vs 32% to 39%, $p = 0.042$), after six months of intervention.

Statins and nonischemic cardiomyopathy

The pleiotropic effects of statins may be beneficial in this group of patients. Indeed, the role of these drugs in patients with nonischemic HF has also been studied in some clinical trials.

In a recent study conducted by Wojnicz et al¹⁵, 74 patients with inflammatory dilated cardiomyopathy and moderate dyslipidemia were randomized to receive atorvastatin 40 mg/day associated with standard HF therapy or only standard HF therapy. Follow-up period was six months. Two patients in the statin group (5.5%) dropped out of the study: one due to gastrointestinal disorders and the other due to a three-fold elevation in transaminases above the upper limit of normal. In the statin group, significant improvements were found in ejection fraction ($p = 0.012$) and functional class ($p = 0.016$). One criticism of this study is the lack of a placebo group, even though the evaluation was blind to the type of treatment given¹⁵.

Another study, this time involving patients with idiopathic dilated cardiomyopathy, ejection fraction < 40%, and NYHA functional class II-III, included 51 patients, who were randomly assigned to placebo or simvastatin (5 mg/day, increased later to 10 mg/day). After 14 weeks, the simvastatin group showed improved NYHA functional class (2.04 ± 0.06 versus 2.32 ± 0.05 , $p < 0.05$) and higher ejection fraction (34 ± 3 to $41 \pm 4\%$, $p < 0.05$), but the placebo group did not. Moreover, plasma concentrations of tumor necrosis factor-alpha, interleukin-6, and atrial natriuretic peptide were significantly lower in the simvastatin group, compared with the placebo group¹⁶.

Lufs et al¹⁷ randomized 15 patients with nonischemic dilated cardiomyopathy and NYHA functional class II-III heart failure to receive cerivastatin 0.4 mg or placebo for about 20 weeks. At study completion, quality of life, measured by a specific questionnaire, and exercise capacity, measured by a six-minute walk test, increased significantly in the statin group, but not in the placebo group¹⁷. The main criticism of this study, in addition to the small number of patients, is the fact that cerivastatin was withdrawn from the market due to the excessive number of cases of rhabdomyolysis related to its use.

Statins and diastolic HF

In a study published in 2005, Fukuta et al¹⁸ evaluated statin administration to patients with diastolic heart failure. One hundred and thirty-seven patients with diastolic HF and ejection fraction $\geq 50\%$ on echocardiogram were analyzed. Follow-up period was 21 ± 12 months, and every patient was medicated according to his/her doctor's prescription. Patients on statins had higher baseline LDL-C than those who were not on statins (153 ± 45 vs 98 ± 33 mg/dL, $p < 0.01$). Once statin therapy was initiated, LDL-C levels fell to values similar to those of patients who were not receiving statins (98 ± 33 mg/dL). After adjustment for clinical variables between groups (hypertension, diabetes, coronary artery disease, and serum creatinine), patients in the statin group showed lower mortality (adjusted relative death risk [95% CI] 0.20 [0.006 to 0.62]; $p = 0.005$). These authors discuss the potential mechanisms by which statins could be beneficial in this population and infer that they are not dependent on LDL-C levels, since these were similar in both the statin and non-statin groups. While this small study raises the possibility of patients with diastolic HF to benefit from their pleiotropic effects, it presents a series of limitations, such as the small number of patients, the nonrandomized use of statin, the fact that baseline and follow-up lipid profiles were not available for all the patients, and the limited statistical power, among other factors.

Future perspectives

Some large-scale studies on HF and statins are currently underway. One of them is the *GISSI heart failure trial*, a large, randomized, double-blind clinical trial designed to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin on morbidity and mortality of patients with symptomatic heart failure¹⁹. Approximately 7000 patients with NYHA class II-IV heart failure and optimized therapy will be enrolled and randomized to n-3 polyunsaturated fatty acids or placebo, as well as to a group of rosuvastatin 10 mg/day or placebo.

CORONA (Controlled Rosuvastatin Multinational Trial) is another important and ongoing clinical trial. This study was designed to determine the effect of rosuvastatin 10 mg/day versus placebo on the combined endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke in patients with symptomatic ischemic cardiomyopathy²⁰.

Conclusions

Statin therapy for HF patients is still a controversial issue. Theoretically, it might be detrimental; however, a number of clinical trials have demonstrated that HF patients may benefit from their use. In any case, we should bear in mind that heart failure itself, with its many etiologies, is a heterogeneous syndrome and that perhaps different subgroups may respond

distinctively to statins. For example, it would be natural to think that administering statins to patients with ischemic HF might be useful, as well as more theoretically substantiated, since the fact that they are beneficial in coronary artery disease is unquestionable. The role of statins in heart failure of other etiologies, in turn, also appears to be beneficial, as was demonstrated by the clinical trials mentioned previously. Even though all evidence points to statins as being a potential new medication in the management of HF, strict clinical trials confirming this hypothesis are still lacking. At present, we believe that statin therapy should be based on LDL-C levels and on risk stratification for atherosclerotic disease of each patient. There is no hard evidence for us to align statins with angiotensin-converting enzyme and beta-blocker inhibitors as a mainstay in the treatment of heart failure of any etiology, independent of LDL-C levels and in the absence of atherosclerotic disease.

Potential Conflict of Interests

Marcio Miname - Received honoraries for reviewing the site of the pharmaceutical industry Pfizer and participates in studies sponsored by laboratories.

Raul D. Santos - Delivers lectures for Pfizer, Merck-Sharp and Astra Zeneca laboratories and participates in studies sponsored by laboratories.

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